Department of Health

The Use of Facemasks and Respirators during an Influenza Pandemic

Scientific Evidence Base Review

May 2014

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Executive summary

Conclusions: Despite a further review of all the available evidence up to 30 November 2012 there is still limited evidence to suggest that use of face masks and/or respirators in health care setting can provide significant protection against infection with influenza when in close contact with infected patients. Some evidence suggests that mask use is best undertaken as part of a package or 'bundle' of personal protection especially including hand hygiene, the new evidence provides some support to this argument particularly within the community or household setting. Early initiation and regular wearing of masks/respirators may improve their effectiveness in healthcare and household settings, again an argument marginally strengthened by the updated evidence. The effectiveness of masks and respirators is likely to be linked to consistent, correct usage and compliance; this remains a major challenge – both in the context of a formal study and in everyday practice. Given the potential loss of effectiveness with incorrect usage, general advice should be to only use masks/ respirators under very particular, specified circumstances, and in combination with other personal protective practices.

Background: Policy makers have been limited by the paucity of scientific evidence upon which to base guidance for use of masks and respirators in healthcare and community settings to reduce the risk of transmission of seasonal and pandemic influenza. It is an area where there has been a considerable amount of new research following the 2009 influenza pandemic. In light of this, the Department of Health (DH) commissioned the Health Protection Agency (HPA) in 2012 to update the scientific review, "The Use of Facemasks and Respirators in an Influenza Pandemic" published in 2011.

Methods: A systematic review of the published literature up to the end of November 2012 was undertaken. This included papers from a search conducted by the original team for the update period, June 2010 to January 2011. The same inclusion criteria and methodology were used. The list of papers generated by the search was sifted for relevance by title, then by abstract and finally by reading the full text to determine whether each article fulfilled the inclusion criteria. Each of the selected papers was summarised and a narrative approach was adopted for data synthesis. As in the previous review, the selected papers underwent a quality assessment process before being included in the final review.

Results: The updated search identified a total of 7841 papers; this included 2173 papers published since the original review in 2011. A total of 95 papers were fully reviewed (23 new papers). Of these papers, 37 met the inclusion criteria (10 new papers) and 25 were included in the systematic review (8 new papers). The 25 papers included twelve (six new) randomised controlled trials (three hospital-based, two community-based and seven household-based studies where interventions were started sometime after exposure in the household) and thirteen (four new) retrospective observational studies. All of the new observational studies focused on influenza (two cohort and two case-control) while the studies from the previous report were all based on SARS in 2003 (eight case-control studies and one retrospective cohort study).

None of the trials found, in the main analyses, a significant difference between non-intervention and mask-only arms (surgical masks or N95/P2 respirators) in either clinically diagnosed (influenza-like-illness/ILI) or laboratory-confirmed influenza. However in four of the household trials, sub-analyses of the datasets revealed some evidence of protection. One trial observed that household contacts who wore a P2 respirator 'all/most' of the time were less likely to develop an influenza-like illness compared to less frequent users. A second trial found a significant reduction in laboratory-confirmed influenza among household contacts that began hand hygiene or hand hygiene plus a face mask within 36 hours of the index case's illness. Two of the new trials identified associations through sub-analyses; for

example a trial in Berlin which considered both seasonal and pandemic influenza found a significant risk reduction in households where masks were used after a per-protocol analysis was applied to the entire dataset. This was the only trial that examined laboratory confirmed pandemic influenza (H1N1 pdm09) in secondary cases. In the other trial, mask and sanitiser use significantly reduced secondary transmission for aggregated outcomes. Additionally a new study conducted in university residence halls identified a significant risk reduction in ILI rates over the intervention period, however this was only observed for the face-mask and hand-hygiene group. Two trials in hospital settings compared surgical masks to N95 respirators. One well-conducted trial compared the protection offered to nurses against influenza infection by either N95 respirators or surgical masks and found that masks were not inferior to respirators. This trial had no control group. A newer study in healthcare workers through sub-analyses found contradictory evidence to suggest that there was a significant protective effect for N95 respirators (non-fit tested) when compared to surgical masks.

Four new observational studies examined mask use as a protective factor against acquiring influenza infection, ultimately providing very little, statistically significant evidence to suggest masks are protective. One of these studies found that there was a significantly lower frequency of H1N1 pdm09 infection in healthcare workers wearing a mask when compared to those not wearing a mask. Furthermore, a sub-analysis of nurses and nurse assistants in a seroprevalence study identified an increased risk of acquiring H1N1 pdm09 infection when not wearing a mask, however while the authors described this result as significant (p-value significant), the confidence interval was not significant. These observational studies contained many limitations and sources of bias making interpretation difficult. The nine other observational studies all investigated the association of recalled use of masks or respirators or other protective behaviours on seeming to acquire SARS. The use of a mask and/or a respirator was found to be independently associated with reduced risk of having had clinically or laboratory diagnosed SARS in five hospital-based and two-community-based studies. However, apart from having to assume findings for this unusual respiratory virus are applicable to influenza, the methodological quality of many of these studies was deficient with controls (and sometimes also cases) lacking microbiological diagnosis and many opportunities for recall bias.

Discussion: None of the studies in the review established a conclusive relationship between mask/respirator use (when used exclusively) and protection against influenza infection. The trial data demonstrated just how difficult and resource intensive it is to undertake these trials in a way that gives useful answers. There is some weak evidence to suggest that facemasks may be protective when they are used early (after recognition of an index case in a household setting); if better compliance (using the masks for longer periods of time) is achieved, and when combined with hand-washing practicing. The inclusion of the new studies marginally strengthens this view. The difficulties in interpreting the observational studies and the relative small number of published studies with outcomes involving microbiologically proven influenza makes it difficult to put any weight towards this type of evidence for supporting policy. Additionally it is questionable how generalisable the SARS studies are for guiding policy on influenza.

Although the use of face masks and/or respirators by healthcare workers when in close contact with patients with pandemic influenza is recommended by the HPA and other public health organizations, a more robust evidence base is desirable. The recent modest increase in both the number and comprehensiveness of trials is encouraging. For example, since the last review there have been six new trials, mainly in the household or community settings. The observational evidence base arising from the 2009 pandemic is still sparse and where studies have emerged, they are limitations and bias issues. Conducting well designed studies in this field are challenging; for example, it may be difficult to design studies employing a control group that does not use any protective equipment including

masks/respirators as such precautions are routinely recommended for pandemic and, in some instances, for seasonal influenza. In addition, more attention is needed to understand the impact of correct usage of masks/respirators (including correct fit and duration of wearing) on effectiveness in blocking influenza transmission.

The Analyses at a Glance - The 12 trials relating to influenza and the 13 observational studies (* indicates new evidence)

Randomised Controlled Trials of Groups

Randomised Controlled Trials in Healthcare settings

First Author, Country, Year of Exposure / Experiment	Methodology and outcome measure	Outcome	Limitations
1. Jacobs, Japan 2009	Block randomisation of a small number of health care workers (HCWs) to wearing or not wearing surgical mask. Outcome measure: self-reported colds.	No significant difference between use of masks or not.	Underpowered study, no exposure data, compliance self-reported.
2. Loeb, Canada, 2008/9	Randomisation of nursing staff to fit-tested N95 respirator or surgical masks. No group not using masks. Outcome measure: microbiologically confirmed influenza.	No significant difference between use of respirators or masks.	Well-designed trial with adequate power but hard to generalise mask wearing given lack of a control arm.
3. McIntyre/ China/ 2008/09*	Cluster, stratified randomised trial of HCWs across hospitals in Beijing. 3 arms including mask group, N95 fit-tested group and N95 non-fit-tested group. Outcome measures: Self-reported CRI, ILI and laboratory-confirmed Influenza.	For all outcomes N95 respirators had lower, but not significant, rates compared with masks. Intention-to-treat analysis found only non-fit-tested N95s protective against CRI. Multivariate analysis (*post-hoc*) found wearing N95s & hospital level each reduced odds of CRI and laboratory-confirmed infection.	Limited power to detect difference between 3 arms, randomisation/ allocation of hospitals in mask-only group.

Randomised Controlled Trials in Household – following diagnosis of influenza in an index case and applying interventions to household members

4.	Cowling, China-HK 2008	Cluster randomisation of households with microbiologically proven influenza cases to: use of surgical masks alone, hand hygiene alone, or no intervention. Outcome measures: microbiologically confirmed influenza (primary) or self-reported influenza symptoms in household contacts.	No significant differences in primary or symptoms outcomes.	Pilot study for Study 5 and so underpowered. Control and hand hygiene arms 'contaminated' by mask wearing. Difficulty in getting intervention started early in intervention household and this will have reduced power.
5.	Cowling, China-HK 2008	Cluster randomisation of households with microbiologically proven influenza cases to: use of surgical masks plus hand-hygiene, hand-hygiene alone, or no intervention. Outcome measures: microbiologically confirmed influenza (primary) or self-reported influenza symptoms in household contacts.	No difference in laboratory confirmed transmission to household contacts. However there was some protective effect when either intervention applied within 36 hours of index case onset in which case significant benefit against influenza symptoms.	Main study following pilot (Study 4). Control and hand hygiene arms contaminated by mask wearing. Difficulty in getting intervention started early in intervention household and this will have reduced power.
6.	MacIntyre, Australia 2006 and 2007	Cluster randomisation of households with microbiologically proven influenza cases households to: use of surgical masks, P2 respirator or no intervention. Outcome measures: influenza-like illness or microbiologically confirmed influenza in household contacts.	No significant differences between the three groups in either influenza like illness or microbiologically confirmed influenza.	Rates of influenza-like illness decreased with consistent adherence, but low level of adherence overall.
7.	Suess, Germany, 2009/10 and 2010/11*	Cluster randomised trial in households with index patients across Berlin. 3 Arms including a hand-hygiene/mask, mask only and	Multivariable analysis showed pooling two intervention groups produced a significant reduction in risk. Also per-protocol analysis of	Underpowered, no additional community exposures assessed, delays between symptom onset and

	no intervention arm. Outcome measure: lab-confirmed Influenza and ILI	data showed significant reductions for mask-only group.	intervention
8. Simmerman, Thailand, 2008/09*	Block randomisation of households with eligible paediatric index patients recruited. Three arms including: hand-hygiene only, hand-hygiene & face mask and education only arm. Outcome measure: lab-confirmed influenza and ILI	Observed a statistically significant increased risk of ILI associated with mask use- opposite direction to hypothesised effect of mask.	Inappropriate randomisation level (not cluster RCT design), no additional community exposure assessment, underpowered, poor adherence in some groups, delays between symptom onset and intervention
9. Canini, France, 2008/09*	Cluster randomised trial in households with index patients across 3 different French regions. 2 arms included mask only and no intervention. Outcome measures: ILI	No significant reduction between arms.	Severely underpowered (early termination of trial), reporting bias, self-reported data, No lab confirmation, blinding methodology, eligibility criteria
10. Larson, US, 2007/08*	Block randomised trial in primarily Hispanic households in upper New York. 3 arms including hand-sanitizer only, hand-sanitizer and face mask, and education only arm. Outcome measure: URI/ ILI/ lab-confirmed influenza	No significant reduction in number of household members reporting secondary cases. However for hand sanitizer and face mask arm a significant reduction in secondary attack rates for all outcomes observed.	Poor self-reported compliance, limited power to detect differences between 3 arms

Randomised Controlled Trials in other community settings

11. Aiello, USA, 2006/7	Cluster randomised trial in students in resident university halls with mask plus hand-sanitizer arm; mask only arm and a no intervention arm. Outcome measure: influenza	Small reduction of approximately 10% in influenza-like illness in both intervention arms compared with no intervention group. Significant ILI reductions observed after week 4 of intervention in students using face	No microbiological confirmation. Hard to generalise to other settings.

	symptoms.	mask and hand-hygiene combination.	
12. Aiello, USA, 2007/08*	Cluster randomised trial in students in resident university halls with mask plus hand-sanitizer arm; mask only arm and a no intervention arm. Outcome measure: influenza symptoms & lab-confirmed Influenza	Significant reduction (60%) in ILI risk after 3rd week of intervention in students in face mask and hand-hygiene group only. No significant reductions for lab-confirmed outcomes.	Follow-up numbers, other community exposures not measured, misclassification bias, reliance on self-reported data, lack of hand-hygiene only group

Observational Studies - Case Control (all retrospective studies on Influenza)

First Author, Country,	Methodology	Outcome	Limitations
1. Zhang, China. 2009/10*	Matched case-control study examining HCWs across Beijing hospitals- cases with lab confirmed H1N1 pdm09. Measured different exposures and personal protective equipment use as potential risk/protective factors	No significant differences was observed for frequency of mask wearing between cases and controls, number of masks used daily or type of mask used. Only significant difference found for control more likely to have received H1N1 pdm09 vaccination.	Exposure measurement issues, self-reported data for behavior, small sample size, recall bias, no lab-confirmation in controls
2. Chokephaibulkit, Bangkok, 2009*	Nested case-control study following a H1N1 pdm09 seroprevalence survey of healthcare identified in 2 Bangkok hospitals. Measured different exposures and 'adherence' to mask use, gloves and hand-hygiene.	Only a sub-analysis revealed nurses/nurse assistants were at a weak, but significant risk of acquiring infection if exposed and not wearing a mask. *However the statistical result produced a significant p-value but non-significant confidence interval for this observation.*	No matching, recall bias, small sample size, interpretation of statistical output/ significance, self-reported data, no monitoring of mask adherence
Observational - Cohort Study (on Influenza)			
1. Balaban, Saudi Arabia, 2009*	Followed a cohort of US pilgrims to the 2009 Hajj. Assessed personal protective behaviors during the Hajj and whether these practices were protective against respiratory illness/ ILI	Practicing wearing a face mask not associated with protective effect: There was an significantly reduced risk of respiratory illness associated with engaging with more protective behaviors	Not a true cohort study (overall study design- 'before & after" study), recall bias, loss to follow-up group not assessed, small sample size, no lab-confirmation
2. Jaeger, USA, 2009*	Retrospective cohort study conducted on HCWs defined as exposed to the first 6 H1N1 pdm09 index patients in health-care settings (Southern California). Serological results compared with HCW work setting, role, and self-reported PPE use.	When Mask or N95 used at any point during exposure to index patients, a significant association was identified with no H1N1 pdm09 infection. Mask or N95 use was also significantly associated with remaining asymptomatic.	Very small sample size, no lab-confirmation, 'PPE use' definition weak, very low response rate and limited data on non-responders

Observational Studies - Case Control (all retrospective studies on SARS in 2003): *Full analysis and details in Annex 5*

First Author, Country,	Methodology	Outcome	Limitations
3. Chen, China	HCWs SARS antibody positive (cases) and negative (control). Exposure was reported use of a double layered vs. a single layered mask.	Double layered mask was protective compared to single layered mask in univariate analysis. No effect on multivariate analysis.	Recall bias possible.
4. Lau, China	HCWs diagnosed with SARS (cases) and asymptomatic HCWs (controls). Exposure was to SARS patients or not and reported use of surgical masks and N95 respirators.	Inconsistent use of masks or respirators not a risk factor for developing SARS in univariate analysis but multivariate analysis found reported inconsistent use of more than one type of PPE was an independent risk for SARS.	No serologic testing of the controls. Reporting bias possible.
5. Nishiura, Viet Nam	HCWs and relatives exposed to SARS patients. Cases were those who were diagnosed with SARS. Exposure was reported use of surgical masks and other personal protection.	Use of masks and gowns was protective on univariate analysis and only masks on logistic regression	No serologic testing of the controls. Reporting bias possible.
6. Nishiyama, Viet Nam	HCWs exposed to SARS patients. Cases were those who were diagnosed with SARS. Exposure was reported use of surgical masks.	Multivariate analysis found significant protection in those who reported always using a mask versus those who reported never wearing a mask.	Possible reporting bias as conducted 7 months after outbreak.
7. Seto, China-HK,	HCWs all exposed to SARS patients. Cases were known infected and controls those without symptoms. Exposure was reported use of masks, respirators, gowns and hand hygiene.	HCWs who reported using a number of protective measures were on univariate analysis less likely to develop SARS. Logistic regression found only use of all types of masks combined was associated with decreased risk.	No serologic testing of the controls. Reporting bias possible.
8. Teleman, Singapore	HCWs exposed to 'super spreader' SARS patients. Cases were HCWs	Reported consistent wearing of respirator and hand washing were	No serologic testing of the controls. Reporting bias

	with SARS and controls those without symptoms. Exposure was reported use of respirators and hand hygiene.	both associated with decreased risk.	possible. No assessment of community / household exposure. No adjustment for confounders.
9. Lau, China-HK	Cases were probable (unconfirmed) SARS cases and controls were asymptomatic people recruited by phone matched for age and sex. Exposure was reported protective behaviours	Wearing a mask in public place, frequent hand washing and disinfecting the home were all protective.	Likely misclassification because no laboratory testing for most cases and no testing of controls.
10. Wu, China	Cases were probable (unconfirmed) SARS cases and controls were asymptomatic people recruited by phone matched for age and sex. Exposure was reported protective behaviours.	Sometimes or always wearing a mask when going out of the house were protective	Likely misclassification because no laboratory testing for most cases and no testing of controls. Recall bias possible.
Observational - Cohort Study (on SARS in 2003): *Full analysis and details in Annex 5*			
11. Loeb, Canada	Retrospective cohort analysis of nurses who entered the room of one hospitalised SARS patient. To assess risk factors for SARS infection, ill nurses with laboratory confirmed SARS were compared to nurses who did not develop illness. Exposure was reported use of mask or respirator.	Reported consistent use of mask or N95 respirator was protective.	Underpowered study. Recall bias possible. Community exposure not explored. No serological testing of controls.

Background

Minimising transmission of influenza requires a range of personal and public health measures taken by individuals and communities such as respiratory etiquette and hand hygiene and possibly proactive school closures (and other measures sometimes called social distancing). Use of personal protective equipment is generally advised according to the risk of exposure to the influenza virus and the degree of infectivity and human pathogenicity of the virus. A particularly vexing issue for policy makers has been the paucity of scientific evidence upon which to base guidance for use of masks and respirators in healthcare and community settings to prevent transmission of seasonal, pandemic and animal influenzas.

The Health Protection Agency (HPA) has undertaken a number of reviews of the effectiveness of face masks. In November 2005 and October 2006 the HPA provided the Department of Health (DH) with two preliminary reviews on face masks for the general public during a pandemic. Subsequently, the HPA was tasked in 2006 by the DH Pandemic Influenza Scientific Advisory Group to review the evidence base for the use of face masks during an influenza pandemic. This review of literature and recommendations relevant to mask/respirator use by the general public and health professionals was published in August 2007 (1). The review found that 'while each of the available studies' methodological approaches preclude firm establishment of a causal relationship between mask use and protection against respiratory illness, an overall impression does emerge, from those studies that examined multiple interventions, that increased utilisation of hygiene measures, such as hand washing, surface cleaning and mask wearing, may reduce the risk of acquiring a respiratory viral infection.' The evidence base regarding the effectiveness of face masks by the general public was observed to be particularly limited. In view of the emergence of 2009 pandemic influenza (H1N1 pdm09) and the availability of new information since the 2007 review, a widely re-modeled review on the topic was conducted by the HPA in November 2009 and updated in 2010 and January 2011.

Given the likelihood of new evidence, especially within a pandemic setting, the Department of Health commissioned the HPA to carry out a further update of the evidence base around the use of masks and respirators that included published articles up to the end of November 2012.

Methods

In line with guidance developed by the HPA, the methodology for this update was tailored to be as robust as possible within the time and resource constraints available.

For the reviews conducted from 2009 - 2011 (Nov 2009, June 2010 & Jan 2011), a consultant epidemiologist with knowledge and experience in influenza Mary Chamberland (MEC) and a researcher/Specialist Registrar in Microbiology Faisal Bin-Reza (FBR) undertook the review (including the first search in Nov 2009). Latterly, colleagues from the European Centre for Disease Prevention and Control (ECDC) in Stockholm, a senior epidemiologist and public health specialist experienced in influenza Angus Nicoll (AN) and a junior epidemiologist Vicente Lopez (VL) helped to undertake the second search (June 2010) and to finalise the review. The same team undertook the update in Jan 2011 in conjunction with the European Centre for Disease Control (ECDC).

For this update, a scientist, Matthew Dixon (MD), with general knowledge in the area of Influenza epidemiology and systematic review techniques was selected to refresh the evidence base with oversight from MEC. In general, the University of York's Centre for Reviews and Dissemination, guidance for undertaking reviews in healthcare was used (2). Work commenced in mid-November 2012 and a draft was available by March 2013 for review by the Department of Health. The final document was submitted to the Department of Health in XXXX.

A series of questions, originally formulated for the 2010 DH review and set in a Population, Intervention, Comparator, Outcomes (PICO) style were developed in the first instance by Dr Jeremy Hawker of the HPA. These questions were modified by replacing 'pandemic influenza' with 'influenza' in all questions to reflect the entire spectrum of influenza (i.e. zoonotic (animal), seasonal and pandemic) for which mask/respirator guidance is applicable.

Consultation was sought from experts at the HPA, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). Replies were received from Dr Carmem Pessoa-Da-Silva of the WHO and Dr Gail Thomson of the HPA who were in agreement with the questions. These questions were reassessed by MD and MEC and consequently deemed appropriate for this update.

The final set of review questions were as follows:

- Does the use of surgical face masks by healthcare workers reduce their risk of contracting influenza (compared to not using a face mask)?
- Does the use of filtration face masks (e.g. FFP3 or N95) by healthcare workers reduce their risk of contracting influenza, particularly for procedures where aerosols are likely to be generated (compared to a surgical face mask)?
- Does the use of surgical face masks by asymptomatic members of the public reduce their risk of contracting influenza (compared to not using a face mask)?
- Does the use of surgical face masks by symptomatic individuals outside the home reduce the risk of transmission of influenza from them to other members of the public (compared to not using a face mask)?

- Does the use of surgical face masks by symptomatic individuals inside the home reduce the risk of transmission of influenza from them to contacts within the home (compared to not using a face mask)?
- Does the use of surgical face masks by asymptomatic carers for symptomatic individuals inside the home reduce their risk of contracting influenza (compared to not using a face mask)?

Inclusion criteria (Figure 1)
The following types of studies, listed in hierarchical order of study design quality, were included (1):

- Randomised controlled trial
  - Randomised cross-over trial
  - Cluster randomised trial
- Quasi-experimental study
  - Non-randomised controlled study
  - Before-and-after study
  - Interrupted time series
- Observational study
  - Cohort study
  - Case-control study

Case series, case reports, mathematical modelling and human/non-human experimental laboratory studies were excluded from the review. Although review articles were not included for analysis, their reference lists were scanned carefully for other potentially relevant studies.

Previous pandemic strains, seasonal influenza A or B viruses and zoonotic viruses such as swine or avian influenza were considered equally acceptable outcomes because mask/respirator guidance is needed for all types of influenza. Studies that evaluated the effect of masks/respirators on transmission of other respiratory viruses were included as a proxy for influenza. Outcome measures were the development of laboratory-confirmed influenza infection (i.e. documented by virus isolation, molecular testing such as polymerase chain reaction and serological studies); clinical influenza-like illness as defined by the investigators was also included but considered to be less specific.

Only studies published in English and which had an abstract were included. Studies in humans were considered directly relevant for the review.

Figure 1. Summary of criteria for the review

Inclusion criteria

- Type of study: randomised controlled trial, quasi-experimental and observational studies
- Participants: humans
- Setting: healthcare or community
- Language: English only
- Abstract: available
- Outcome: laboratory-confirmed or clinically diagnosed influenza and other viral respiratory infections

Exclusion criteria

- Type of study: case series, case report, mathematical modelling and human/non-human experimental laboratory studies, reviews
- Participants: animals
- Setting: laboratory
- Language: non-English
- Abstract: not available
- Outcome: bacterial infections

Search strategy

The search strategy focused on systematic reviews and primary studies taking into account the PICOs detailed above. Filters for study design and type of outcome measurement (e.g. laboratory confirmed infection versus clinical illness) were not included in the search strategy.

We have built upon the findings from the 2010 DH review. This update therefore includes an analysis of the previous findings alongside the updated findings from; 1) ECDC update in Jan 2011 (published Dec 2011) and 2) the most recent update with searches conducted by MD (search run in Dec 2012). The time frames for 1) and 2) are as follows:

1. An initial update was conducted by the ECDC for the 6-month period following the last DH report in June 2010, capturing new literature between ***June 2010*** and ***January 2011***. The review methodologies and findings of the ECDC update can be found in the *Influenza Journal* (3).

2. For this latest update, MD conducted a literature search on 12 December 2012 with a time period restriction between ***12 July 2010*** (*ensuring a 6-month overlap since the last search conducted in January 2011, also effectively covering the search period for search #3*) and ***30 Nov 2012***.

Annex 1 details the search terms used for searching the PubMed database. In addition, the following databases were searched: Bandolier, the Cochrane Library Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment database, the NHS Economic Evaluation database, the UK Database of Uncertainties about the Effects of Treatments, the NHS Centre for Reviews and Dissemination and the Cumulative Index to Nursing and Allied Health Literature, the Excerpta Medica Database, and Scopus. Annex 2 details the terms used for these searches.

Other sources

A limited effort was made to identify studies apart from those published in the peer-reviewed literature; ECDC's Antimicrobial resistance and Health Care Associated Infection Programme was consulted and MEC's and AN's hardcopy literature files (for the original DH report) were hand-searched to identify additional published and unpublished articles or other documents of relevance.

Study selection, data extraction and quality assessment

For the purpose of this update, MD completed the main elements of the systematic review to capture new evidence since the ECDC January 2011 search.

Study selection was conducted in two stages. Firstly, papers identified by the search were initially scanned and excluded by MD on the basis of the 'title' for relevance to the review. The principal objective was to identify studies that appeared to meet the inclusion criteria. In addition, some papers that did not meet the inclusion criteria (e.g. animal and human and non-human experimental laboratory studies of mask/respirator properties, commentaries or reviews of influenza transmission or pandemic influenza) were selected to provide useful background or supplemental information. Finally, any relevant systematic or narrative reviews were selected. The full text of all these articles was then sought.

Data from the selected papers was extracted using a pre-designed form (Annex 3) created on a Microsoft-excel spreadsheet program. Data elements on the form included publication information, study characteristics, participant characteristics, the intervention and setting, outcome and results. MD performed the initial data extraction of the full article and made an initial determination regarding its eligibility for inclusion in the review. MEC reviewed the full papers in conjunction with the data extraction forms, supplemented MD's initial abstraction and re-assessed each paper for inclusion in the review. Any differences were resolved by mutual agreement. MD assessed the quality of the eligible studies using the Critical Appraisal Skills Programme tools for randomised controlled trials, case control studies and cohort studies (http://www.phru.nhs.uk/Pages/PHD/resources.htm)

Data synthesis

A synthesis of the data, combining both the updated evidence and previous report findings was developed by MD. The synthesis was restricted to a narrative approach that included an analysis of the relationships within and between studies and an overall assessment of the robustness of the evidence and limitations of both the studies and the evidence review (2). In addition, the synthesis considered the implications for policy and guidance development as well as future research.

Results

This section captures all data from the four searches undertaken (two from the original DH report- searches 1 & 2 and two new – searches 3 & 4) and all the evidence from these searches has been assessed in this review.

Search 1. November 2009: The initial search identified 5351 papers. On the basis of 'title' for relevance to the review (Figure 2), 5041 papers were excluded. Abstracts for the remaining 310 papers were reviewed and a further 256 papers were eliminated.

The 54 remaining papers consisted of 21 papers selected by both MEC and FBR; 18 papers selected by FBR and not by MEC; and 15 papers selected by MEC and not by FBR. Full copies of these 54 papers plus five papers identified from scanning the reference lists of review papers and one paper retrieved from MEC's hardcopy files (a recent publication not indexed in PubMed) were reviewed and abstracted.

Search 2. June 2010: This search identified 317 papers; after excluding the non-relevant ones and the ones already considered in the previous search, 14 extra papers were considered for inclusion. Of these, two were excluded as they lacked an abstract, three were excluded because they were reviews and eight not meeting the inclusion criteria were excluded. Only one extra paper was included after the second search.

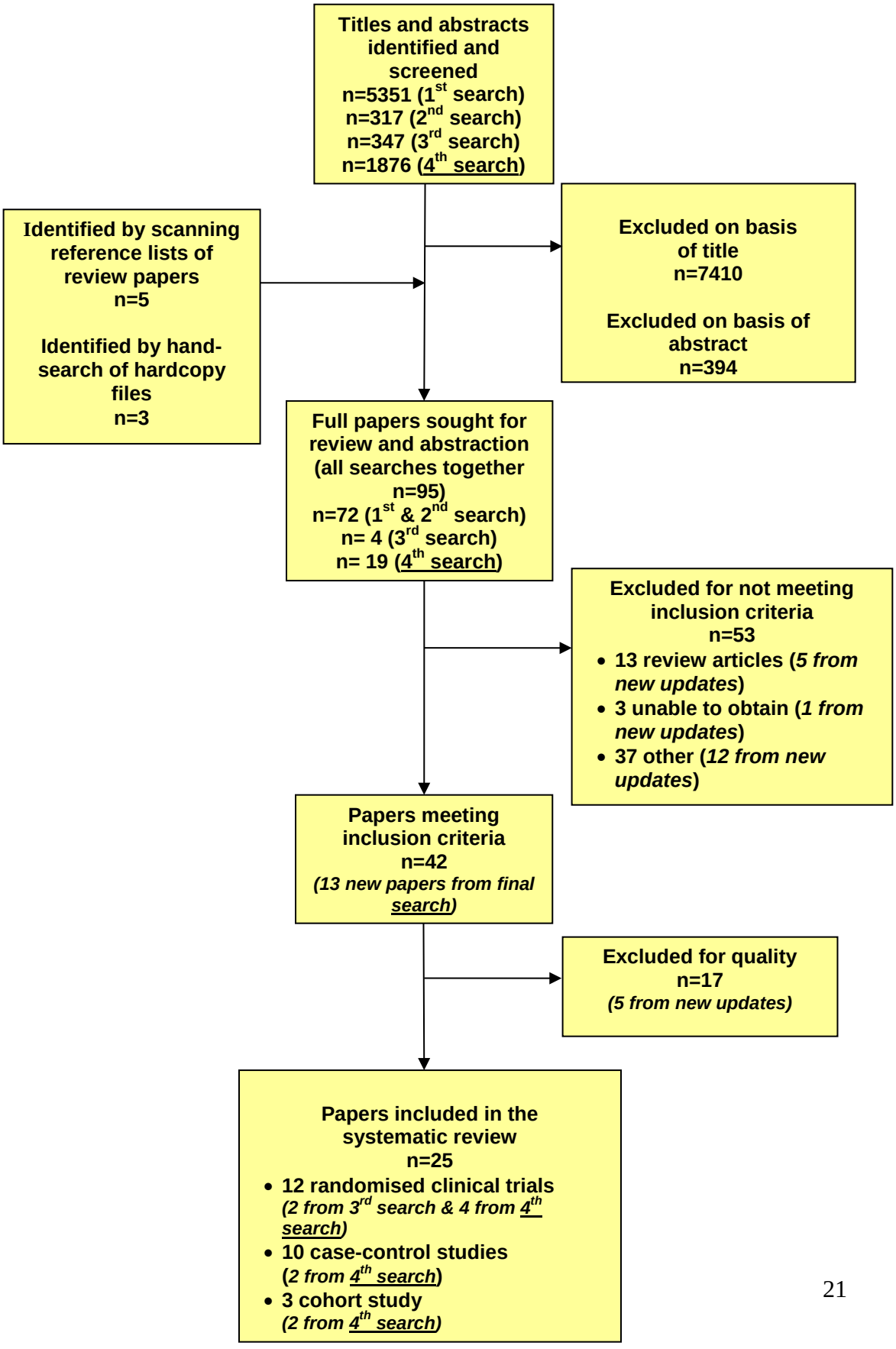
Search 3 January 2011: This search identified 347 new papers which, after assessment, yielded four new papers for full review. Two of these were excluded (either not meeting complete inclusion criteria or quality control) leaving two new papers - both randomised control trials. These two new studies are considered in the final updated systematic review.

Search 4 December 2012: The most recent search identified 1684 papers and following exclusion of non-relevant and previously considered papers, 19 new papers were included for full-review. A further 11 papers not meeting the inclusion criteria were excluded. The remaining eight new papers were included in the systematic review- a mixture of randomised control trials and observational studies.

A total of 95 papers were sourced for full review across the four searches (table 1 providing a classification of the 95 papers that were read in their entirety and abstracted). Papers that were finally excluded (meeting the inclusion criteria but excluded on quality or where it was impossible to interpret the impact of masks from other interventions are described in Annex 4. Reviews included in the full text review but excluded from the final systematic review are analysed in the discussion section (five new reviews).

The descriptions, results and limitations of the studies focussing on influenza specifically are laid out in Table 2. The observational studies focussing specifically on SARS were so diverse complex and difficult to analyse that they were further described in more detail in Annex 5.

Figure 2. Diagram of search strategy results and article selection (*studies from this specific update work- or search #4- underlined*)



After abstraction of the results of all searches, 37 papers were classified as meeting the inclusion criteria. Twelve of these papers were excluded subsequently because it was not possible to distinguish the effect of mask or respirator use from other types of personal protective equipment and/or infection control measures such as hand hygiene (54-70); five new studies were also excluded because of quality at this stage (66-70). All 17 papers excluded for quality have been analysed in annex 4.This left 25 papers for inclusion in the final systematic review. The studies consisted of 12 RCTs and 13 observational studies (10 case-control studies and three retrospective cohort studies). Details of the studies specific to influenza (12 RCTs and four observational studies) are summarised in Table 2, while studies specific to SARS are analysed in Annex 5 (9 observational studies).

Table 1. Combined results for 95 papers selected for full-review by type of paper

Classification	Total number of papers from previous DH report (included)	New papers from 2011 ECDC update (included)	New papers from 2012 update (included)	Number included in the final systematic review
Randomised controlled trial	7 (6)	2 (2)	4 (4)	12
Quasi-experimental study	5	0	0	0
Observational study	23 (9)	0	9 (4)	13
Case report or case series	2	0	2	0
Mathematical model	1	0	0	0
In vitro experimental laboratory study or animal study	12	0	0	0
Systematic review	7	1	1	0
Narrative review	3	1	2	0
Background/supplemental information	9	0	0	0
Unable to obtain	3	0	1	0
Total	**72 (15)**	**4 (2)**	**19 (8)**	**25**

Randomised controlled trials

Three of the randomised trials were hospital-based studies (4, 5, 6), seven were conducted in household settings (7-9, 12-15) and two were in university halls of residence (10,11). Overall, none of the trials found any significant differences within the main analyses with respect to either clinically diagnosed or laboratory-confirmed infections with influenza or other viral respiratory pathogens when assessing mask and non mask use. However, there was some evidence of protection when sub-analyses were performed in four of the household studies (8, 9, 12, 15). Additionally, one trial found a significant reduction in ILI rates over the study period when mask use was combined with hand hygiene compared to the control arm (11).

One of the three hospital-based studies was a small, block randomised trial of two groups of healthcare workers in Japan (masks versus no masks) and found no difference in the frequency of self-reported cold symptoms (4). A second study undertook a non-inferiority randomised trial comparing N95 respirators and surgical

masks in protecting healthcare workers against laboratory-confirmed influenza infection using 446 nurses in emergency departments and medical and paediatric units in eight tertiary care hospitals in Ontario (5). Participants were allocated to wear either a fit-tested N95 or a surgical face mask when providing care (including aerosol generating procedures) to patients with a febrile respiratory illness during the influenza season. No difference in influenza infection was detected in the two groups. The final hospital based study stratified 1441 health care workers across 15 Beijing hospitals to analyse the effectiveness of surgical masks compared to both fit-tested and non-fit tested N95 respirators (6). The wearers of N95 respirators had lower, but non-significant attack rates, compared to those wearing surgical masks. However the intention to treat analysis (when adjusting for clustering of hospitals) identified that non-fit-tested N95s had a statistically significant protective effect against clinical respiratory illness when compared to surgical masks in healthcare workers. Additionally a multivariate analysis (*post hoc*) found that wearing any N95 mask type protected against clinical respiratory illness.

Randomised trials in household settings have been undertaken in Hong Kong, Sydney, Beijing, New York, Berlin, Bangkok and across urban centres in France. The designs are similar with early identification of individuals in households and then random allocation of all family members to specific interventions or none (control households).

Cowling and colleagues, building on the lessons learned from a smaller pilot study (7) conducted a large cluster randomised trial of households in Hong Kong to evaluate use of face masks and hand hygiene by household contacts to prevent influenza transmission. Participants were allocated to 3 arms: controls, surgical face masks plus hand hygiene or hand hygiene alone (8). Although there was no statistical difference in secondary attack ratios of influenza among household contacts of the index cases in the three groups, a significant reduction in secondary attack ratios among household members was detected if either intervention was applied within 36 hours of the index case's onset of illness.

A cluster randomized controlled trial in Australia compared household contacts of paediatric index cases (0-15 years) with a febrile respiratory illness that were randomised to control, surgical mask or non-fit-tested P2 respirator intervention groups (9). No differences in rates of influenza-like infection or rates of respiratory virus isolation were observed in an intention-to-treat analysis. In a survival analysis that evaluated risk factors for influenza-like illness, use of P2 respirators or surgical masks grouped together was found to significantly reduce the risk for illness in those household contacts who reported wearing the device 'all' or 'most' of the time for the first five days; however, the study was underpowered to detect a difference in efficacy between P2 and surgical masks.

A study in Berlin, conducted across two influenza seasons (2009/10 and 2010/11), randomised households to three groups; control, face mask or face mask and hand-hygiene with the analyses stratified by influenza type (seasonal or pandemic cases), season, and early implementation of interventions (12). This was the only example of a trail that analyzed specific H1N1 pdm09 secondary household attack rates. In the intention-to-treat multivariable analysis, pooling of both intervention groups resulted in a significant reduction in lab-confirmed influenza when stratified for either early intervention or pandemic-only cases; however there was no statistically significant effect of intervention groups on secondary household attack rates. When a per-protocol analysis was applied the odds ratios in both the mask-only and mask/hand-hygiene

groups were between 0.2 and 0.3 suggesting a strong protective effect. Although a statistically significant reduction was found in the mask-only groups.

Simmerman et al assessed hand-hygiene or hand-hygiene/face mask intervention arms against controls (education but no intervention) in Bangkok, Thailand (13). The study recruited 422 eligible pediatric index patients with ILI (later tested for influenza by laboratory confirmation) with households randomly allocated to intervention arms. After multivariable analysis, there was no protective effect against secondary influenza infection between arms. The authors suggested that lack of protective effect may be explained by the observation that index patients slept in the parent's bedroom in 90% of households (thus exposing the parents because the masks were not worn at night), which may have consequently negated any impact of wearing the mask during the day.

Larson and colleagues examined hand-sanitiser and hand-sanitiser/mask use (both with education) effectiveness amongst crowded households in upper Manhattan (15). In this study, both household caretakers and symptomatic individuals were asked to wear masks. The study found that mask wearing coupled with hand-sanitiser use significantly reduced secondary transmission of aggregated upper respiratory infection/ ILI and lab-confirmed influenza outcome compared with control households (education but no intervention) in the final logistic regression model. Unfortunately there was not a mask-only group, but the observation that hand sanitizer alone resulted in no reduction in the aggregated outcome suggests that mask use, in combination with hand-sanitiser had an impact on transmission. There was also limited power to detect differences amongst the three groups and there was also observed cross-contamination with use of hand-sanitizer in the control group.

The final randomised trial in the household setting was set in three French regions during the 2009-10 influenza season (14). Following recruitment of eligible index patients after a home medical visit, households were randomized and then allocated to either surgical mask or control (no-intervention) arms. The use of face masks in this trial directly attempted to assess the ability of masks to reduce transmission from a symptomatic individual (in this case the index patient) to household contacts. There was no difference in secondary illness amongst household contacts between the trial arms, however the study suffered from significant underpowering (38% power to detect the 10% hypothesized difference) since only 30% of the required households were enrolled. The authors attributed the low levels enrollment to both a mild/short influenza season and the onset of pandemic influenza in 2009, forcing the study team to prematurely terminate the trial.

Two cluster parallel randomised control trials were carried out in university residence halls. The first study assessed the impact of face masks and hand hygiene on the incidence of ILI symptoms during the 2006-07 influenza season (10). It had three arms: control (no intervention), mask plus alcohol-based sanitizer and mask-only. The survival analysis undertaken with the 368 participants that met the definition for ILI (the main outcome) found that both intervention groups had an approximate 10% reduction in the cumulative ILI incidence compared with the control group in unadjusted analyses, although this difference was not statistically significant. When covariates were adjusted for in this analysis, a significant reduction in ILI rates was observed for the mask and hand-hygiene group only when compared to control, after four weeks of the intervention. The same team updated this randomised trial during the 2007-08 influenza season, this time including lab-confirmed influenza outcomes (11). Again, a statistically significant ILI

reduction of 75% (for mask and hand-hygiene only compared to no intervention) was observed in the adjusted models, this time from week 3 onwards. For the face mask only group, a reduction in risk was observed for ILI rates but this was not significant. The cumulative ILI rate ratios only reduced (non-significantly) for the mask and hand-hygiene intervention over the study period. When assessing lab-confirmed influenza rates, a cumulative reduction of 43% lab-confirmed influenza in the mask and hand-hygiene intervention (compared to no intervention) and 8% reduction in the mask-only intervention was observed, however none of these results proved statistically significant.

Observational studies

There were four studies that examined mask use as a protective factor against acquiring influenza infection. Two of these studies were cohort studies and two case control studies - one a nested case-control within a survey. Three were conducted in healthcare settings (16-18) and one in a specialised community setting (19).

Zhang et al conducted a 1:4 matched case control studying face mask use among healthcare workers across 25 Beijing hospitals (16). The study identified exposed cases as those with lab-confirmed H1N1 pdm09 and previously interacting with patients (with respiratory infections) while controls were defined as individuals with no lab-confirmed H1N1 pdm09 or ILI but exposed to patients with respiratory infections. Individuals were then asked to provide information on a range of behaviours seven days prior to symptom onset, including high risk procedures, hand-washing practices, use of other personal protective equipment (including masks) and seasonal/pandemic influenza vaccination status. There was only a marginal difference in the number or frequency of masks used between cases and control and this was not significant. It was also reported that controls had a significantly higher level of pandemic influenza vaccination in comparison to controls; the only statistically significant protective factor in the multivariate analysis. Given the study design, it was very difficult to attribute influenza infection in cases to exposure with patients suffering from respiratory symptoms, and furthermore the study failed to measure non-occupational or community exposures.

Chokephaibulkit et al undertook a seroprevalence survey of the healthcare workers in two large public tertiary care hospitals in Bangkok, Thailand after the peak of the 2009 pandemic in the region (17). A nested case control study to examine risk factors for H1N1 pdm09 infection compared case healthcare workers (as indicated by a heamagluttination inhibition [HI] assay with antibody titres >40) to controls (HI assay titre <40). Neither wearing a mask (N95/ surgical mask) nor frequency of mask use was associated with protection against Influenza infection. The authors state that a sub-group analysis showed an increased risk of infection amongst nurses and nurse assistants when not wearing a mask during close contact with other healthcare workers (suffering from ILI). However this observation must be viewed with caution because the authors provide a statistically significant p value (0.039) but a non-significant confidence interval (95% CI 0.9-5.6).

One retrospective cohort study examined whether healthcare workers wearing personal protective equipment were less likely to acquire influenza in comparison to healthcare workers not wearing personal protective equipment during exposures to the first 6 lab-confirmed H1N1 pdm09 index cases in southern California (18). A total of 63 healthcare workers were identified as exposed to these index cases. The study team then collected detailed information on exposures including self-reported personal protective use when in contact with index cases. Dividing the 63 individuals into whether they were ‘exposed’

or ‘not-exposed’, based on whether they used the personal protective equipment, the researchers assessed whether there was a difference in frequency of seropositive H1N1 pdm09 cases between the groups. It was observed that there was a statistically significant difference in H1N1 pdm09 infection between individuals wearing masks at any point and those not wearing masks (0% seropositive individuals when using either surgical masks or N95 respirators in comparison to 14% individuals in the no mask/respirator group). The study however lacked power to detect significant differences between those wearing N95 respirators against those wearing surgical masks. In addition to this the study suffered for a large number of other limitations such as potential measurement and recall bias.

Finally for studies focusing on influenza, a prospective cohort study (19) was conducted to assess personal protective practices amongst US pilgrims to the 2009 Hajj mass gathering event. Participants were recruited from a number of sites in two US states and administered a pre-Hajj questionnaire and post-Hajj questionnaire, assessing levels of respiratory illness and ILI during the event. Wearing a face mask was not protective against respiratory illness, only social distancing (as defined by the CDC/WHO community mitigation practice guidelines) was associated with reduced respiratory illness amongst pilgrims. Engaging in more protective practices such as hand-hygiene, face mask use and social distancing (when practices were assessed as continuous variables) was also associated with reduced occurrence of respiratory illness. The lack of lab-confirmation made it impossible to evaluate whether protective practices were associated with reduced influenza occurrence and reliance on self-reported data, with the possibility of recall bias severely restricting the utility of the study findings.

The nine remaining studies (20-28) evaluated face mask and respirator use following the outbreaks of severe acute respiratory syndrome (SARS) in 2003; seven studies were conducted among healthcare workers and two were community-based. These studies, specific to SARS were included in the original DH review as the only evidence base for observational study type. However the emergence of observational studies specific to influenza has reduced the need to focus so heavily on the SARS studies; consequently the appraisal and analysis of these papers have been transferred to Annex 5.

It should be noted that while studies on SARS sheds some light on this topic area, using these studies to inform policy on use of masks and respirators face for influenza transmission faces two fundamental problems. Firstly SARS is an unusual acute viral respiratory infection with a very different epidemiology to almost all other respiratory viral infections, including human influenza. It rarely infects children, has a long incubation period, transmits little early on, mostly transmits in health care settings and is not prone to global spread. To date it has only appeared once and depending on the authority consulted was either containable or simply self-limiting. Secondly, the studies are often poorly designed and the results difficult to interpret. A number lack microbiological confirmation of cases or controls and it is possible that a number of the SARS cases were not cases at all. Since all the cases knew they were cases recall bias is highly likely. .

Table 2. Synopsis of studies evaluating face mask and respirator use included in the final review

RSV= respiratory syncytial virus; HCW=healthcare worker; PPE=personal protective equipment; ILI=influenza-like illness; CRI= clinical respiratory illness; URI= upper respiratory infection; CPI=cardiopulmonary resuscitation; ICU=intensive care unit; CCU=coronary care unit; RT-PCR= reverse transcription- polymerase chain reaction; H1N1 pdm09= 2009 pandemic influenza; RCT= randomised control; HH= Household

A. Randomized controlled trials

Investigator (Reference no.)	Study design and participants	Reported results	Comments
Jacobs et al., 2009 (4)	Block randomized trial of HCWs in Japan allocated to 2 arms: mask group (17 HCWs) who wore surgical mask while on hospital property serving in their role as HCW and no mask group (15 HCWs) who refrained from wearing unless required as part of their job (e.g. surgical nurse). **Outcome measure:** self-reported cold symptoms scaled to severity.	No difference between two groups; 1 cold reported in each arm; higher severity scores reported in HCWs living with children 84.3% of participants reported full compliance with mask use and nonuse	**Reviewer:** Limitations include lack of exposure data for hospital or community; compliance self-reported and not differentiated by intervention arm; no confirmatory laboratory testing performed; no data to indicate sensitivity and specificity of cold symptom severity scale used **Author**: Study underpowered to detect difference; small number of participants who were difficult to recruit; mask wearing limited to hospital; data on mask wearing in community not reported
Loeb et al., 2009 (5)	Non-inferiority randomized trial of 446 nurses in emergency departments and medical and paediatric units in 8 tertiary care hospitals in Ontario allocated to two arms: fit-tested N95 respirator group or surgical mask group when providing care (including aerosol generating procedures) to patients with febrile respiratory illness during the 2008-20009 influenza season. **Outcome measure:** laboratory confirmed influenza	No difference in influenza infection between two groups: 50 (23.6%) of 212 in surgical mask group versus 48 (22.9%) of 210 in the respirator group (absolute risk difference, 0.73%; 95% CI -8.8%-7.3%; p=0.86) Very limited audit found high	**Reviewer**: Strengths include well designed trial with adequate power; clinically ill HCWs self-swabbed for PCR testing and serological testing sought for all HCWs (symptomatic and asymptomatic); no differences between two groups for potential confounders for influenza infection (i.e. receipt of influenza vaccine, ILI

	measured by PCR or serology.	rates of mask/respirator compliance in both groups	in child, spouse or housemate, type of hospital unit) Limitations include lack of a control group (e.g. HCWs who cared for patients with no respiratory illness) and lack of detailed patient exposure (type and frequency) information **Author:** Strengths include individual- and hospital-level randomization; comprehensive laboratory-confirmed outcome assessment; follow-up over an entire influenza season and high rate of participant follow-up Limitations include incomplete assessment of compliance with mask/respirator wearing; potential confounding due to indirect contact transmission as hand hygiene and use of gowns and gloves not monitored, although glove and gown use was standard practice in study hospitals (e.g. if N95 group had worse adherence would have biased towards noninferiority); inability to determine if influenza acquired due to hospital or community exposures, however HH data suggests exposures balanced in each group

Aiello et al., 2010 (10)	Cluster parallel randomized control trial carried out in the community among 1297 young adults living in university residence halls to assess the impact of face masks and hand hygiene on the incidence of ILI symptoms during the 2006-07 influenza season, with three arms: control or nonintervention group (552 students), mask plus alcohol-based sanitizer group (367 students) and mask-only group (378 students). **Outcome measure:** self-reported ILI symptoms based on clinical ascertainment or survey report.	Cluster adjusted X^2 p-value (comparing proportion of positive samples across study groups) = 0.44. The survival analysis undertaken with the 368 participants that complied with the main outcome (i.e. had ILI) showed that both intervention groups showed an approximate reduction of 10% in the cumulative ILI incidence compared with the control group in unadjusted analyses. **Discrete time analysis for each week showed significant reductions (in adjusted models for covariates) from week 4 of the intervention in the mask and hand-hygiene group only when compared to the control group** (ILI reductions from 35% (confidence interval [CI], 9%–53%) to 51% (CI, 13%–73%)	**Reviewer:** Strengths include the way the study was randomized, the method used for observing compliance with the study and the attempt at studying the effect of combining the use of masks with hand hygiene. As limitations, the lack of significance in the results adds to the lack of power of the study 'per se'. **Author:** Limitations - Much of the data on natural infection derives from studies of SARS and the transmission characteristics of this pathogen may be different from those of influenza. Influenza incidence was low, so it is likely that most ILI cases were not associated with influenza infection. The study was underpowered to detect low reductions in the rate of ILI and across study arms. Strengths include that there were no significant differences in rates of ILI across the 7 residence halls at baseline, suggesting that naturally occurring differences in ILI rates across halls are unlikely to explain the findings. The magnitude of the design effect for both the adjusted and unadjusted models was well below 1 suggesting a lack of significant clustering of ILI by

			residence hall. Given the limited age range and specialized living setting of study participants, the results cannot be generalized to other, non-university aged, community-dwelling populations.
Cowling et al., 2008 (7)	Cluster randomized trial of HHs (including index case and HH contacts) in Hong Kong allocated to 3 arms and analysed as: control (71 HH and 205 contacts), surgical face masks (both index patient and HH contacts) (21 HH and 61 HH contacts) or hand hygiene (30 HH and 84 HH contacts). **Outcome measure:** laboratory culture-confirmed influenza (primary); clinically diagnosed influenza by self-reported symptoms (secondary).	No difference in laboratory-confirmed secondary attack ratios in controls 0.06 (95% CI 0.03–0.10), face mask 0.07(95% CI 0.02– 0.16) and hand hygiene groups 0.06 (95% CI 0.02–0.13), p=0.99. Compliance low: 45% (21%) of index cases (HH contacts) reported wearing mask often/always.	**Reviewer:** Strengths include analyses adjusted for influenza vaccination history and age/sex of index case. Trial limited in distinguishing relative contribution of mask wearing by the index cases versus the HH contacts in observed secondary attack ratios. **Author:** Strengths include randomized allocation, laboratory-based outcome measurements. Limitations include pilot study underpowered to detect differences in interventions; secondary attack rate lower and dropout rate higher than anticipated; control and hand hygiene arms 'contaminated' by use of masks by more than 25% of index cases.
Cowling et al., 2009 (8)	Cluster randomized trial of HH (including index case and HH contacts) in Hong Kong allocated to 3 arms and analysed as: control or no intervention (91 HH and 279 contacts), surgical face masks (both index patient and HH contacts) and hand hygiene (83 HH	No difference in laboratory-confirmed secondary attack ratios in controls 10% (95% CI 6–14), hand hygiene 5% (95% CI 3-9) and face mask plus hand hygiene	**Reviewer:** Strengths include collection and testing of respiratory samples from both symptomatic and asymptomatic contacts; independent and objective

	and 258 HH contacts) or hand hygiene (85 HH and 257 HH contacts). **Outcome measure:** RT-PCR positive confirmed influenza (primary); clinically diagnosed influenza by self-reported symptoms (secondary).	groups 7% (95% CI 4– 1); p=0.22. Significant reduction in secondary attack ratio if either intervention applied within 36 hours of index case's onset. Adherence low: 49% (26%) of index cases (HH contacts) reported wearing mask often/always in the mask plus hand hygiene arm.	assessment of adherence (e.g. count masks, weigh soap and alcohol). Trial limited in distinguishing relative contribution of mask wearing by the index case versus the HH contacts in observed secondary attack ratios **Author:** Limitations include 'contamination' of control group as 15% (7%) of index cases (HH contacts) reported wearing mask often/always; cannot precisely distinguish between relative contributions of hand hygiene and facemasks as they were combined; potential bias from recruitment of symptomatic index cases: may have led to increased HH transmission due to possible higher viral shedding (not measured); delay between onset in index patient and start of interventions may have underestimated true effects of interventions; and if HH contacts more likely to have pre-existing immunity, may have reduced observed effect

MacIntyre et al., 2009 (9)	Cluster randomized trial of HH (index case and HH contacts >16 yrs) in Sydney Australia allocated to 3 arms and analyzed as: control or no intervention (50 HH and 100 contacts) or surgical mask (47 HH and 94 contacts) or P2 respirator (46 HH and 92 contacts). **Outcome measure:** ILI or laboratory confirmed respiratory virus infection.	No difference in ILI rates in controls 16 (16.0%) of 100, in surgical mask group 21 (22.3%) of 94 (RR 1.29, 95%CI 0.69-2.31, p=0.46) and in P2 respirator group 14 (15.2%)of 92 (RR 0.95, 95%CI=0.49-1.84, p=1); no difference in respiratory virus isolation rates in controls 3 (3.0%) of 100, in surgical mask group 6 (6.4%) of 94 (RR 2.13, 95%CI 0.55-8.26, p=0.32) and in P2 respirator group 8 (8.7%) of 92 (RR 2.90, 95%CI 0.79-10.6, p=0.12). Reduced risk for ILI associated with adherent mask or respirator use (hazard ratio 0.26, CI 0.09-0.77, p=0.015). Adherence low: 21% of contacts in the surgical mask and respirator arms wore mask often/always	**Reviewer:** Strength: Groups well balanced with rates of influenza immunization in index child and adults in HH, index child attendance at childcare and duration of illness and ILI in siblings. Limitations include opportunities for bias as interval between index case diagnosis and start of intervention not specified; contacts had swabs during follow-up only if developed symptoms, thus asymptomatic infection under-estimated; adherence self-reported; no data on use of antivirals for index patients. **Author:** Study underpowered to detect difference in efficacy between surgical mask and respirator arms.
Aiello et al, 2012 (11)	Cluster RCT: students recruited within university residence halls. Randomisation at residence house level (37 residences and 1111 eligible participants: 938 considered ILI-free for analysis). 3 groups (control or no intervention, face mask only, hand-hygiene and face mask) – 370/349/392 participants in each arm for analysis. Based on data from previous year (Aiello et al, 2010) calculated 87% power to detect reduction of 25% (RR=0.75) or greater in	***From week 3 onwards statistically significant reduction in ILI risk*** (adjusted RR 0.40 p-value 0.01) in face mask and hand-hygiene group only. In face mask only group an increasing reduction in risk to week 3 was observed (RR 0.85 in week 3) in adjusted models but	**Reviewer:** Strengths: randomisation methodology and improvement on previous study (Aiello et al, 2006) & lab-confirmation. Limitations include: (1) At conclusion, only 93% accounted for in control/ face-mask only groups

	illness rates between intervention and control groups. Intervention period lasted 6 weeks from recruitment. A*nalysis assessed non-symptomatic students wearing masks.* **Outcome measure**: ILI and lab-confirmed influenza between arms	RR but non-significant. The cumulative RR showed a protective, non-significant effect (RR 0.78) against ILI for face mask and hand-hygiene group only (adjusted models). 43% reduction in lab-confirmed influenza in face-mask + hand-hygiene group (adjusted RR 0.57) and 8% reduction in facemask only group (adjusted RR 0.92) however neither stat significant (p= 0.16/0.69). In the face mask + hand-hygiene group: masks on average were worn 5.08 hrs per day and in the mask only group 4.49 hrs per day. There was no significant difference in levels of mask use between the intervention groups	and 96% in face mask + hand-hygiene: no assessment into differences in these individuals, (2) Lack of significance in results adds to lack of power of study 'per se'. **Author:** (1) Possible those participants with ILI who tested negative for influenza were infected with other respiratory viruses.(2) Participants only advised to wear masks in residence halls- may have been external community exposures (not measured) (3) No hand-hygiene only group therefore unable to detangle combined effects of mask and hand-hygiene (4) Reliance on self-reported data (*reporting and recall bias*) (5) Generalisability limited to similar settings
Suess et al, 2012 (12)	Single-blind, cluster RCT: 111 Households across Berlin recruited after eligible index patient identified (by general practitioners) at evenly distributed sites around the city. Recruitment occurred over two consecutive influenza seasons (Nov 2009- Jan 2010 & Jan-April 2011). Once households recruited, observation lasted 8 days following full intervention implementation. 3 arms (control or nonintervention /112 participants, mask only/95, hand-hygiene + mask/95) & a total of 111 households randomised. *All household members required to use masks.* **Outcome measure**: primary: lab-confirmed (RT-PCR) and secondary outcome: self-reported ILI.	In the multivariable analysis; ***When the data for both mask* only and *mask & hand-hygiene pooled, a statistically significant risk reduction was observed vs. lab confirmed influenza*** (OR 0.16 & p= 0.04). Also the OR for secondary lab confirmed infection was significantly lower in the separate mask + hygiene and pooled intervention groups for index cases with H1N1 pdm09 (*sub-analysis*).	**Reviewer:** Strengths: lab-confirmation, serial testing of household members and low contamination across groups Limitations: (1) No details of whether all households completed follow-up period (2) Underpowered- only 84 households included in final analysis and power calculations required 114 households (3) Exposure may have occurred in wider community (only proxy measure for this was 'time spent at

		In a per-protocol analysis (full adherence to facemask use) - All OR of both mask only and mask + hand-hygiene were below 1. ***Significant protective effect observed in mask only group when analysing complete set of data*** (all influenza subtypes). Authors concluded daily adherence was good, reaching a plateau (>50% face mask use) in both intervention groups across two seasons. Lower adherence in 2010/11 for mask+ hand-hygiene group.	home') **Author:** (1) Noticeable delays between symptom onset of index patient and implementation of intervention (possible under-estimation of true effect) (2) Cannot determine if possible protective effect attributable to face mask use by index or contacts (3) Household contact lab-testing only examined whether contact infected with virus subtype of index patient - may have underestimated number of secondary cases (4) Monetary incentives and frequent household visits may have influenced behaviour- reflects real practice?
Simmerman et al, 2011 (13)	Block randomisation of households recruited within Bangkok after eligible paediatric patients identified (those seeking medical treatment for ILI symptoms at a hospital outpatient setting). 348 households and 885 participants eligible for analysis. Study period conducted between April 9, 2008- August 13, 2009 and post-recruitment of a household, intervention period lasted 21 days. 3 trial arms (hand-hygiene only, face mask + hand-hygiene, control or education-only). 119HH/302 members in control arm, 119HH/292 members in hand-washing only arm, 110HH/291 members in hand-washing + face mask arm. *All household members used interventions.* **Outcome measure:** Secondary attack rates in household contacts measured by lab-confirmed influenza and ILI	In the multivariable analysis: There was no significant risk reduction across the different arms (for the hand-hygiene + face mask group an adjusted OR 1.16 p= 0.525 vs. control) - in fact there was a slight, non-significant, increase in risk. In a sub-analysis looking at early implementation (<48hrs) this was also a slight increased (non- significant) risk in intervention arms (adjusted OR for secondary infection 1.06 in hand-washing only and 1.15 in hand-washing & mask). However there was an ***observed (significant) increased risk for***	**Reviewer:** Strengths: lab-confirmation outcome Limitations: (1) No cluster RCT design- given the randomisation unit was at household level, (2) A number of households did not complete follow up in each arm- no of analysis whether the covariate factors differed in these groups (3) No description of blinding methodology for clinicians (4) Underpowered- did not reach number of households as determined by power calculations **Author:** (1) No assessment of

		ILI outcome in both intervention groups: (i.e. adjusted OR 2.15/ p= 0.004 for hand-hygiene and mask group). This result is ***over two-fold in the opposite hypothesised direction of effect***. Adherence was variable across groups- parents wore masks for a median of 153 minutes per day, far more than other relations (median 59 minutes per day), index patients (median 35 minutes per day) or siblings (median 17 minutes per day).	exposure risk outside of the household (2) The study complicated by onset of H1N1 pandemic influenza in June 2009- subsequent national hygiene induced behavioural changes in control group (3) Delays in implementation after index case symptom onset (4) Poor adherence in some groups (index cases and younger siblings in particular)
Canini et al, 2010 (14)	A cluster RCT: recruited eligible index patients and households across three French regions during the 2008-2009 influenza seasons. Intervention period for 5 days after medical visit. A referent household member was assigned to report/take measurements during this period. Trial arms included mask only and control (no intervention) arm. Study however stopped prematurely in March 2009 following onset of pandemic influenza and low seasonal activity: only 30% HH recruited *Only index cases used interventions.* **Outcome measure:** % of HH contacts developing ILI following 5 days from start-date. In addition, a more sensitive ILI case definition used.	In the multivariate analysis: There was no significant risk reduction between arms (adjusted OR 0.95/ p= 0.90). Using a more 'sensitive' ILI case definition did not modify this. Also, the proportion of households with one or more secondary cases did not differ between arms. In all sub-analyses(early implementation): was significant reduction in risk between arms Index cases reported wearing the mask 2.5 (±1.3) masks per day and for a duration of 3.7 (±2.7) hours a day. 66% of households in the intervention arm reported wearing face mask more than	**Reviewer:** Limitations: (1) Reliance on a household 'referent' to collect data during the period and perform a final interview at the end of the period to present all the household information on ILI symptoms etc- unreliable measurement methodology (2) No statistical analysis to determine whether baseline covariates differed between arms (3) Clinicians not blinded to allocation only investigators recording results from household referent (4) Only >5yr olds eligible as an index patient however evidence suggest younger age groups important for household transmission. **Author:** (1) Only 30% of the

		80% of the anticipated duration.	intended households were recruited- this only produced 38% power to detect the hypothesised difference of 10%.- study was significantly underpowered (2) No lab-confirmation- missed asymptomatic & sub-clinical cases
Larson et al, 2010 (15)	Block randomisation of 617 urban Households during 2007/08 Influenza season. 174 households allocated into control (education only) group; 169 households to hand sanitiser group; and 166 households to hand sanitiser and mask group; household caretaker to wear mask when within 3 feet of person with ILI for 7 days or until symptoms disappeared and to change mask between interactions; ill person encouraged to wear mask when within 3 feet of other household members. **Outcome measure:** Self-reported ILI/URI symptoms and viral culture.	Hand sanitiser group more likely to report no symptomatic HH members (545/946 [57.6%] compared with education (447/904 [49.4%] and hand sanitiser/mask (363/938 [38.7%] groups, P <0.01; no significant differences in rates of URI, ILI or influenza infection by intervention group in multivariate analyses. ***Hand sanitiser/mask group had significant reduction in secondary attack rates for URI/ILI/influenza infection*** (OR 0.82, 95% CI 0.70–0.97) compared with education. No reduction with hand sanitiser alone (OR 1.01, 95% CI 0.85–1.21).	**Reviewer:** Limitations: (1) Poor self-reported compliance with mask use: 22 (50%) of 44 HHs reporting ILI used masks within 48 hours of episode onset; average of 2 (range 0–9) masks/day/ILI episode used. (2) Limited power to detect differences amongst 3 groups; some use of hand sanitiser in control group in response to media reports about methicillin-resistant Staphylococcus aureus.
McIntyre et al, 2011 (6)	Cluster, stratified (by size of hospital and level of infection control) randomisation of 1441 HCWs in 15 Beijing hospitals into 1) mask group (492 HCWs/5 hospitals); 2) N95 fit-tested group (461 HCWs/5 hospitals; and 3) N95 non-fit-tested group (488 HCWs/5 hospitals); supplemented with convenience	For all outcomes N95 respirators had lower, but not significant, rates compared with masks. ***Intention-to-treat analysis adjusted for clustering of hospitals found only non-fit-***	**Reviewer:** Limitations: (1) Monitored and self-reported compliance good (68–76%) in the 3 arms; however, monitoring by HCWs' supervisors not optimal method (2) Limited power to detect

	sample of non-mask-wearing HCWs from 9 hospitals; participants wore the mask/respirator on every shift for 4 consecutive weeks after being shown when/how to wear it. **Outcome measure**: Self-reported CRI, ILI and laboratory-confirmed viral infection by PCR.	***tested N95s protective against CRI*** (16/488 [3.3%], OR 0.48, 95% CI 0.24–0.98, P =0.045) compared with mask group (33/492 [6.7%]) as ref. Multivariate analysis found wearing N95s and hospital level each significantly reduced odds of CRI and laboratory-confirmed infection (post-hoc analysis adjusting for confounders).	differences amongst 3 groups as observed attack rates low. (3) Authors note 46% probability of incorrectly finding one significant difference. Despite stratified randomisation, mask group comprised of only level 3 (most sophisticated) hospitals. (4) Hard to generalise beyond unique study population. (5) Detailed data on potential exposures and information on community levels of influenza not provided

B. Observational: case-control study

Investigator (Reference no.)	Study design and participants	Reported results	Comments
Zhang et al, 2012 (16)	A matched (1:4) retrospective case-control study looked at HCWs across 25 Beijing hospitals (51 cases and 204 controls) from August 2009 to January 2010. Matching was done by hospital, ward, age and gender. Cases were lab-confirmed H1N1 pdm09. Controls were ILI and lab-confirmed diagnosis negative. Recruitment and data collection was conducted in February 2010- a questionnaire assessed characteristics/ exposures 7 days prior to symptom onset (matched controls assessed for same 7 day period).	No significant differences was observed for frequency of mask wearing between cases and controls (72.5% vs. 71.6% p= 0.344 wearing medical mask >80% of working time), number of masks used daily (p value 0.798). No significant difference between types of mask used in case/control groups compared to 'never used a mask'. Only significant association (post-adjustment for confounders) indicated that control HCW's were more likely significantly to have received the pandemic vaccine: (OR 0.15, 95% CI 0.047-0.479, p=0.001).	**Reviewer:** Strengths: lab-confirmation- reduced chance of misclassification of cases Limitations: (1) No mention of refusal rate in controls (2) Exposure' classification different between cases and control (within 2m for cases, no distance of exposure for controls) (3) Self-reported information of mask use (4) No specific monitoring of mask adherence **Author:** (1) Recall bias likely: recruitment occurred at least 1 month after exposure period (2) Sample size relatively small (n=255): reduced ability to detect difference (3) No lab-confirmation in controls: misclassification bias (4) No measurement of community exposure
Chokephaibulkit et al, 2012 (17)	Seroprevalence survey conducted amongst HCWs during peak of the 2009 pandemic outbreak (June-Aug 2009) from two large hospitals in Bangkok. HCWs invited 1 month after peak of outbreak with approx a third of HCWs from a range of different wards invited. Self-administered questionnaire (exposures to patients/PPE behaviours assessed) and blood taken for HI assay. A nested case-control study	Univariate analysis revealed that there was no significant difference between a) mask types used between seropositive cases and controls. For both surgical mask and either type of mask use among HCWs there was a non-significant increased	**Reviewer:** Limitation: (1) No matching of controls to cases (2) Recall bias because exposure/behaviour could have occurred 2-3 months prior to questionnaire (3) Serological test may have picked up vaccination- large assumptions about acquiring recent pH1N1 infection with this methodology

	conducted (Antibody titres >40 defined as a 'seropositive case' assumed to have a recent H1N1 pdm09 infection) to examine PPE behaviours between 'cases/controls'. 256 HCPs participated: 33 (13%) seropositive 'cases- recent infection' and 226 (87%) non-seropositive 'controls- no recent infection'.	risk of acquiring infection (N95- crude OR 1, surgical mask- crude OR 1.2 p= 0.73), b) The frequency of mask use between cases and controls was in addition not associated (>90% crude OR 0.9, p = 0.86, 70-90% crude OR=1) A sub-analysis of ***nurses/nurse assistants revealed a weak risk of acquiring infection if not-wearing mask after close contact with a HCW*** (OR 2.3, CI 0.9-5.6, p= 0.039): conflicting statistical output however.	**Author:** (1) Small sample size (2) Self-reported data collection for behaviours/exposures & not validation/verification of answers/ questionnaire (3) No monitoring of mask adherence

C. Observational: cohort study

Investigator (Reference no.)	Study design and participants	Reported results	Comments
Balaban et al, 2012 (19)	Authors define this as a prospective 'cohort' study: pilgrims recruited at multiple sites across Michigan and Minnesota before travelling to the 2009 Hajj (Nov 25-29 2009). A pre-travel survey was conducted to collect information on baseline data (Oct 21- Nov 18 2009) and a post-travel survey for respiratory symptoms and personal protection behaviours (Dec 3 2009- Feb 8 2010). A total of 221 completed pre-travel survey and 186 completed post-travel (84.2% response rate).	Practicing wearing a face mask was not associated with a reduced risk: 41.6% practiced wearing a face mask and had respiratory infection (RI) vs. 39.7% not wearing a mask & with respiratory infection (OR= 1.42, 95% CI 0.7-2.88, p= 0.21) When protective behaviours were assessed as continuous variable, there was an significantly reduced risk of respiratory illness associated	**Reviewer:** Limitations: (1) Potential for recall bias in post-travel surveys, especially in surveys conducted in Jan-Feb 2010. (2) Overall study design not a prospective cohort but really a 'before and after' study- lack of unexposed control group. (3) No assessment on 15.8% of cohort either loss to follow up or refusing to complete post-travel questionnaire- differ from the rest of the cohort? (4) Small sample size **Author:** (1) Study population possibly not representative on Muslim population of US(2) All health &

		with engaging with more protective behaviours (F=3.13 p=0.03) No protective behaviours were associated with less severe respiratory illness.	behaviour information self-reported via questionnaires (although questionnaire validated by multiple sources)
Jaeger et al, 2012 (18)	Retrospective cohort study conducted on HCWs (inpatient and outpatient settings) after exposure to the first 6 lab-confirmed H1N1 pdm09 index cases in southern California. Exposure period after interaction with index patients presenting between March 28- April 22, 2009. HCWs identified as exposed if within 6m of index patient or direct contact. Participants were administered questionnaires (initial interviews conducted 3-30 days since last index patient encounter with an additional 2-week follow up interview) to identify more detailed information on exposures and self-reported symptoms. Paired serum samples for lab confirmation also collected. Of 139 initially identified as potentially exposed, 63 recruited in final cohort.	16% of exposed cohort met criteria for post-exposure ARI and 10% for ILI while 14% of cohort was seropositive for pH1N1. ***Mask or N95 use during index patient encounters was significantly associated with no H1N1 pdm09 infection.*** 0% of HCWs reporting mask/N95 use became seropositive while 21% reporting no mask/N95 use became seropositive (p=0.047). Mask use during 100% of exposures was not significantly different between those and became sero-positive, and those who didn't and became seropositive (p=0.18). Mask and N95 use also significantly associated with remaining asymptomatic (p=0.03).	**Reviewer:** Strengths: Data collected on community exposures Limitations: (1) Very small total cohort/sample size (n=63) (2) No mask adherence monitoring (3) Reliance on self-reported data **Author:** (1) Limited power prevent separating effect of N95 or surgical masks (2) Interviews conducted by hospital staff which may have prevented full disclosure on HCWs symptoms while working or on non-compliance with PPE. (3) Data collected on non-occupational exposure identified two HCWs with potential community exposures. (4) Low response rate (45%) limited study power (5) No data available for non-responders (6) Reclassification of post-exposure period for symptom onset of up to 10 days instead of 7- increase chances that exposure could be up to three days after designated exposure (i.e. from elsewhere)

Table 3. Summary of case control studies evaluating mask/respirator use (influenza)

Investigator (Reference no.)	Type of mask evaluated	Interval from outbreak to study	Exposure information	Evaluation of potential confounding factors	Case and control issues	Reported results
Zhang et al, 2012 (16)	N95 respirator, medical/surgical mask or cloth mask	Exposure period: August 2009 to January 2010. Recruitment and data collection conducted in February 2010 (2-5 months interval).	HCWs: contact with patient (respiratory infection) within 2m in the public hospital, and diagnosed with H1N1 pdm09 (RT-PCR). Conduct of high-risk procedures (procedure likely to generate respiratory aerosols). No non-occupational exposures documented.	Matching (1:4) on factors: hospital, ward, age and gender. Cases/controls excluded if household member with ARI/ lab-confirmed H1N1 pdm09 Univariate and multivariate logistic regression conducted to determine risk factors associated with infection.	No mention of refusal rate in controls. 'Exposure' classification different between cases and control. Recall bias- likely to be greater in controls. No lab-confirmation in controls (misclassification bias)	No significant difference for frequency of mask use, number of masks used or types of mask between cases/controls. Only significant factor post-adjustment for confounders was HCW's significantly more likely to have received the pandemic vaccine
Chokephaibulkit et al, 2012 (17)	N95 respirator or surgical mask	HCPs who worked during peak of 2009 pandemic (June-Aug 2009)- data collection 1 month after peak of outbreak (1 month interval).	HCWs: contact with patients (suspected H1N1 pdm09) categorised as every time (>90–100%), mostly (70–90%), and <60%. Non-occupational exposures documented: household member sick or visiting crowded places (both during outbreak period).	No matching (retrospective nested-study) Collected other information on potential hospital exposures and non-occupational exposures Univariate analysis initially performed then multivariate analysis (multiple logistic regression) on factors associated with	No matching of controls to cases, definition of recently acquired H1N1 pdm09 infection 'cases' using serology, recall bias because exposure/ behaviour could have occurred 2-3 months prior to questionnaire	Univariate analysis revealed that there was no significant difference between mask types, the frequency of mask A sub-analysis of nurses/nurse assistants revealed a weak risk of acquiring infection after close contact with a patient and not-wearing mask (although confidence interval not significant). Visiting crowded public places

	seropositive cases	during the outbreak also associated with acquiring infection

HCW=healthcare worker; PPE=personal protective equipment; RT-PCR= reverse transcription- polymerase chain reaction; H1N1 pdm09= 2009 pandemic influenza

Discussion

All the systematic searches of the literature have identified a limited number of studies that examined the use of face masks or respirators by healthcare workers, by household contacts of a symptomatic patient and by asymptomatic members of the public to reduce the risk of contracting influenza. We did not find any studies across all of the searches that focused specifically on use of face masks by asymptomatic home carers of ill patients.

Since the HPA last reviewed the evidence base in June 2010, several new studies have been identified, including six new randomised control trials and four observational studies. On the one hand it is encouraging that interest in this topic has led to a number of new studies; on the other, there remains a relative paucity of good evidence to help address important public health questions around mask and respirator use. The new evidence on the whole has not dramatically modified the findings since the last DH report. One key difference was the identification of observational studies that focussed on influenza, whereas the previous report relied exclusively on observational studies examining SARS.

What does the evidence tell us about mask/respirator use to reduce the risk of influenza transmission?

None of the studies in the review established a conclusive relationship between mask/respirator use and protection against influenza infection. There remains a significant challenge to demonstrating a protective effect in a scientific study as well as realising it in 'real world' situations.

Given the intrinsic differences in transmission risks of influenza in healthcare and non-healthcare settings it is prudent to consider these two settings individually.

Healthcare setting

There is a clear lack of randomised control studies within healthcare settings. Since the last review in 2010, there has been one new randomised control in a hospital environment. While this study found a protective effect for N95 respirators when compared to surgical masks, the association was not statistically significant (6). However an intention-to treat analysis showed a significantly protective effect against clinical respiratory infection with non-fitted N95 respirators in comparison to surgical masks. However the study was underpowered to detect any more than a minor superior efficacy of N95 respirators. This evidence somewhat conflicts the findings from the Canadian trial (5) that found similar rates of laboratory-confirmed influenza in nurses who wore surgical face masks and in nurses who wore respirators. Although trial had many strengths in it's methodology, it was not designed to answer the question whether the use of face masks or respirators reduced the risk of contracting influenza compared to no use. Unfortunately, the authors did not include an analysis of influenza infection rates among nurses who performed aerosol generating procedures stratified by type of respiratory protective device.

A final trial conducted in Japan examined a small number of healthcare workers to assess whether a surgical mask would be protective against self-reported cold symptoms when compared to no mask and found no difference in frequency (4).

A case-control study conducted in healthcare workers across Beijing hospitals failed to show a noticeable difference between cases and controls when considering mask use (16).

Two observational studies specifically focusing on influenza in healthcare settings provided some limited evidence for face mask mediated protection for healthcare personnel. A seroprevalence survey of healthcare workers in Bangkok (17) demonstrated that nurses and nurse assistants were at an increased risk of acquiring pandemic influenza when not wearing a face mask (after being exposed to other health-care workers with ILI), however the statistical significance and interpretation remains highly questionable. A cohort study amongst exposed health-care workers in southern California observed a significant difference between the reduced numbers of lab-confirmed cases of H1N1 pdm09 in healthcare personnel wearing masks during any encounter with ill patients when compared to those not wearing masks (18). These observational findings conflict with the randomized trial findings for no protective effect of wearing a face mask in the Japanese trial (4). However throughout the observational studies (16-18) there were a number of significant methodological issues. Therefore this evidence should be used with caution in healthcare settings when asserting whether general utilization of masks provides protection for healthcare personnel against influenza or whether respirators provide superior protection to surgical masks.

The remaining studies investigated the effect of masks/respirators on transmission of SARS which has behaviours that renders it different from influenza (see Annex 5). However since most of the SARS transmission was in health care settings special attention should be paid to their findings for nosocomial spread. Mask and/or respirator use was an independent protective factor against clinically or laboratory-diagnosed SARS in five studies (22-26). In addition, a randomised trial of masks versus no masks for cold symptoms found that wearing a double layer cotton mask was protective in the univariate but not the multivariate analysis (20). The findings suggest that for a respiratory virus such as SARS coronavirus, the use of surgical masks or respirators may be protective. However, when attempting to apply the findings from the SARS studies to influenza recommendations it should be noted that there are differences between the viruses hat need to be taken an account of. In addition to this, the methodological quality of many of these studies was poor making interpretation difficult (Annex 5)

Community settings

The evidence for face mask use in communities focussed on three specific types of settings including households, university halls of residence and the Hajj mass gathering event.

If we first consider household settings, the results from randomised control have failed to find any conclusive evidence that households with surgical face mask use provide protection when compared to households without the intervention- this is evident for both ILI and laboratory-confirmed influenza (7-15). However, sub-analyses from four of the larger studies found evidence of effectiveness; this includes two of the new studies (8, 9, 12, 15). McIntyre et al found a significant protective effect if household contacts were consistently adherent in wearing the mask or respirator (9). Cowling also found a positive protective effect if contacts started wearing a facemask soon after the index case in the household was identified (8). Two new studies found evidence from sub-analysis of the main data, however these associations were a result of combining sub-

sections of the data in pooled analyses. For example, the household trial in Berlin (12) found that masks were significantly protective against lab-confirmed infection when a per-protocol analysis was applied to the dataset (after combining seasonal influenza and H1N1 pdm09 data). Larson et al (15) identified a significant association between the hand-hygiene/mask group and a reduction in secondary household attack rates when using aggregated outcomes (combining URI, ILI and influenza episode data). Hand-sanitizer only interventions did not result in a reduction, suggesting that the combined effect of the interventions reduced transmission. This is despite Larson et al reporting relatively poor compliance. Although subject to some inevitable opportunities for bias, in general the trials were well-designed. However six (including a feasibility pilot for a larger full-scale study) of the seven were underpowered to detect differences in the different study arms (the study by Canini et al (14) provides an extreme example of under powering, only achieving 38% power for detecting a hypothesized 10% reduction the between intervention (face mask) and no intervention arms). Therefore these limitations within the household trials reduce the validity and strength of the evidence base.

Secondly, within a university residence hall setting Aiello et al (10, 11) demonstrated that across two influenza seasons; 2006-07 and 2007-08 reductions in influenza-like illness were observed. However a statistically significant reduction was only observed for the combined face-mask and hand-hygiene group after 4 weeks from the implementation start date in the 2006-07 influenza season (10) and after 3 weeks in the 2007-08 season (11). The authors noted that their study may have been better positioned to identify a protective effect for mask and hand hygiene use because participants initiated the interventions at the beginning of the influenza season. However after careful review of the study design, it is clear that transmission could have occurred amongst contacts before interventions were implemented. This is because interventions were only initiated in the residences after identification of a laboratory-confirmed index case. However the findings from Aiello et al (11) provides some cautious evidence to suggest combined impact of hygienic interventions in the community may provide some protection to non-symptomatic individuals.

Finally, an observational study in the specialized community setting of Hajj demonstrated that wearing face masks alone was not protective (19), although this evidence has limited applicability to other settings. Furthermore this prospective cohort study had numerous biases and limitations.

There is therefore some tentative evidence across community settings to suggest that facemasks may protect when interventions are administered early, when full adherence is achieved or when combined with other hygienic practices such as hand-washing. However, in the case of the household studies, making inferences from sub-analysis data is risky because smaller samples are used to conduct the analysis and statistical power is therefore reduced. The university residence hall trials found significant protective effects in the main analyses, but this was only for the combined hand-hygiene and face mask intervention.

Practical implications of the review's findings

There is a limited evidence base to support the use of face masks and/or respirators by healthcare workers when in close contact with patients with pandemic influenza. Nonetheless, prior to and during the 2009 pandemic, public health organisations and other professional bodies had to use the available information to develop

recommendations about their use. Information about the effectiveness of masks and respirators in preventing transmission of influenza is a critical foundation, although not the only factor taken into account when formulating advice and guidance. The DH/HPA's updated pandemic H1N1 pdm09 influenza guidance for infection control in healthcare settings recommends that surgical masks be worn when working in close contact (within approximately one metre) of a patient with symptoms (29). An FFP3 respirator is recommended when undertaking aerosol-generating procedures. Similar recommendations were advocated by the WHO (30). In contrast, the U.S Centers for Disease Control and Prevention (CDC) adopted more stringent recommendations advocating the use of respiratory protection at least as protective as a fit-tested N95 respirator for healthcare personnel who were in close contact with patients with suspected or confirmed pandemic H1N1 pdm09 influenza (31). Their recommendation do not represent a different interpretation of the available evidence, rather they cited the unique circumstances associated with the 2009 pandemic at the time (e.g. low levels of population immunity including those in the age range of healthcare personnel, the availability of vaccination well after the start of the pandemic and the increased risk for complications of influenza in some healthcare personnel such as pregnant women). CDC recommendations continue to promote that healthcare personnel wear surgical face masks when entering the room of a patient with suspected or confirmed influenza (according to the occupational seasonal influenza prevention guidance- 32). Respirators are recommended when aerosol generating procedures are performed. Our review provides very little evidence to suggest that surgical masks protect healthcare workers (only one study showing no protection against cold symptoms- 4). There is also conflicting evidence to demonstrate that respirators are more effective in blocking transmission than surgical face masks (5, 6). A number of studies show the protective effect of wearing a mask or respirator against SARS, but this virus is very different from influenza and the strength of evidence is diminished because of the low quality of these studies.

Evidence for the effectiveness of masks and respirators to prevent influenza transmission is even less compelling for non-healthcare settings. There are however a larger number of randomised control trials conducted in community settings. Some limited evidence hints at the potential impact of face masks in the community (household or university residence hall type settings) for reducing the risk of transmission when interventions are applied early (8, 12, 14), although the lack of significance in two of these studies reduces the strength of evidence. All things being equal, masks and respirators would be expected to have similar benefits in protecting a susceptible individual when exposed to a patient with influenza in a setting such as a household. However, a number of factors influence the potential effectiveness of a mask/respirator in reducing influenza transmission and some of these would likely differ in healthcare and community settings (1). For example, healthcare workers would be expected to receive formal training in the correct use of mask/respirators; although participants in these research studies were instructed in the proper use of a mask or respirator, it may not have been as extensive or re-occurring compared to a hospital setting. Training outside of a research study would be even less predictable. Safe use of a mask/respirator is linked to access to hand hygiene facilities before donning and after removal of the device as well as to receptacles for disposal; access to these facilities may be more limited in a community setting. Masks/respirators might have to be worn for much longer periods of time in a household or similar setting where there is the potential for prolonged, regular contact with the infected patient. In contrast, healthcare workers'

use of masks/respirators is typically episodic; i.e. when they have close contact with a specific patient.

An important factor in all of these studies is compliance and correct usage. It is difficult to achieve in a healthcare setting despite external prompts (e.g. posting of signs, positioning supplies of masks/respirators at the entrance to patient rooms); compliance in a community setting is all the harder. Compliance relates to adherence of the intervention where it is considered necessary whereas the correct usage refers to whether the intervention is implemented correctly i.e. does the mask fit to the face.

Compliance (also termed adherence in many studies) with mask or respirator use was variable across the community-based randomised trials. A number of these studies demonstrated poor-compliance amongst household members. Studies (7-9) conducted in community settings showed that no more than about a quarter of contacts were fully adherent in wearing masks/respirators. In one study, rates of self-reported adherence were found to decline over a 5-day period (9). In Cowling's two studies, it was demonstrated that index cases were more likely to be adherent than household contacts (7, 8). Larson et al (15) in contrast reported poor compliance- only 50% of households with ILI reported wearing masks within 48 hours of episode onset. Adherence to mask wearing may possibly reflect a societal view on mask wearing. In Hong Kong mask wearing was hard to stop while in Australia mask wearing was uncommon in the culture.

However a range of community studies demonstrated improved compliance with face mask use. The study conducted in France (14) reported good self-reported face-mask use with 66% of households documented as wearing masks for 80% or more of the anticipated duration. Self-reported mask adherence was evidently higher amongst certain individuals in the Bangkok study (13), namely those with greater index case contact such as parents. However the authors identified that use of personal hygienic practices (especially hand-washing) may have increased in the later stages of the study across all trial arms as a direct result of increased public awareness and public health campaigns during the early stage of the 2009 Influenza pandemic in Bangkok. Suess et al (12) reported good levels of adherence across all groups (adults, children, contacts and index cases), an observation measured by both self-reported data and calculation of remaining intervention materials for each household at the end of the study period. Only in the mask and hygiene group for the 2010/11 influenza season were the adherence levels notably reduced. Finally, Aiello et al (10, 11) reported improved mask compliance (both self-reported and observations made by trained trial staff) in intervention groups during the later stages of the study. This behavioral change was attributed to an improved public health campaign following spring break in an attempt to remind students about the use of masks.

Compliance was better among healthcare workers compared to household contacts, but methods to assess this were not optimal across the three hospital-based studies (4-6). For example, both monitored and self-reported compliance was improved in the Beijing study with 68-76% for healthcare workers wearing either surgical or N95 fitted/non-fitted masks, however the monitoring methodology by supervisors was acknowledged as sub-optimal (6). Some of the results for the community level settings indicate that adherence/compliance can be achieved to an acceptable level, however the difficulties with accurately capturing data by self-reported approaches are clear (10,-12, 14-15).
Even in the context of a clinical trial where one might expect optimal compliance, investigators encountered disappointing rates of adherence. Nonetheless, improved

compliance and early application of interventions are ways in which effectiveness could be improved.

The onset of a pandemic would inevitably increase the use of personal protective equipment within the wider population as a result of a greater perceived risk. For example, the influence of the 2009 influenza pandemic likely directly impacted hand-hygiene practices (in particular) during the Bangkok household trial (13). Subjects in the no intervention arm reported washing their hands only slightly less than the intervention arms. However while mask use may increase amongst the wider public during a pandemic, ensuring masks are properly used, if such a policy were to be introduced provides a greater challenge for public health authorities.

One issue not explored in any great detail is the correct usage of masks/respirators during the studies. Only McIntyre et al (6) examined the effectiveness of fit-tested N95 against non-fit tested, identifying, surprisingly, only non-fit tested N95 respirators as significantly protective in the intention to treat analysis. Further research should focus on this aspect.

The lack of demonstrable effectiveness of mask and respirators in community settings coupled with the aforementioned implementation issues is likely reflected in the varying advice that public health organizations have developed for community use of masks/respirators during the 2009 pandemic. For occupational settings other than healthcare, the DH/HPA advised that consideration might be given to using a face mask if close proximity (less than a metre) with an individual with symptoms consistent with an influenza-like illness is inevitable (33). Similarly, the WHO acknowledged that individuals may wish to wear masks in the home or community setting, particularly if they are in close contact with a person with influenza-like symptoms; e.g. while providing care to family members (34). However we have not been able to identify any studies for individuals at increased risk of exposure to symptomatic individuals outside of a healthcare setting (i.e. carers in a care home) so are unable to strengthen these comments with evidence. CDC advised that the use of face masks and respirators in community and home settings during the 2009 pandemic was generally not recommended but could be considered for persons at increased risk of severe illness from influenza (35).

It is important to note three additional considerations when assessing the practical implications of the review's findings. Firstly, development of evidence-based guidance about mask/respirator use is inextricably linked to what is known about how influenza is spread and specific risk factors that can affect transmissibility (e.g. host factors, pathogen factors, environmental factors and particle size) (1). This is an area equally fraught with uncertainty and limited and conflicting evidence regarding the relative importance and frequency of the four possible modes of transmission - direct contact, indirect contact, droplet and aerosol (36, 37). In the context of the 2009 pandemic, the HPA and the DH have articulated a view that transmission appears to be similar to seasonal influenza; i.e. occurring mainly through the spread of respiratory droplets. Accordingly, droplet precautions (which include use of a face mask) are recommended (29). Since transmission via aerosols may occur, especially when associated with the performance of aerosol-generating procedures in healthcare settings, more rigorous infection control measures are recommended, including the use of an FFP3 respirator (29). However, it should be noted that there are no studies comparing rates of influenza

infection in workers who wore surgical face masks versus those who wore respirators during such procedures.

Secondly, although the focus of this review has been on masks and respirators, limiting transmission of influenza in both healthcare and community settings requires a multifaceted approach, of which masks and respirators are but one component. The evidence base for community settings suggests that face masks, when combined with hand-hygiene practices often provide some level of protection, more so than when just one intervention was applied independently (8, 11, 15). In the healthcare setting this 'hierarchy of controls' includes administrative controls to help reduce the introduction and spread of infection (e.g. policies to restrict entrance of ill visitors and workers, vaccination of healthcare workers); environmental/engineering controls (e.g. adequate ventilation) and lastly, use of personal protective equipment and hand hygiene (29). In the community setting a similarly structured approach is advised. However, during both the planning for an eventual pandemic and the subsequent public health response to the 2009 pandemic, concern over policy and guidance related to mask/respirator use has at times seemed to overshadow other important controls (38).

Thirdly the policy, guidance and recommendations on mask/respirator use and other infection control measures has to be seen in the context they are being used and the primary purpose of the activities where they are being deployed. For example one simulation study found that proper application of one set of guidance would compromise normal ward functioning in a UK hospital setting (39).

In the vast majority of studies in this review, mask/respirator use was not the only control measure in place or under evaluation. For example, several of the recent randomised trials in community settings have included hand hygiene either alone or combined with respiratory protection (7, 8, 10, 11, 13 & 15). Healthcare workers invariably used multiple measures such as hand hygiene, gowns, and gloves in addition to masks/respirators; this was particularly evident in studies conducted during SARS and the 2009 pandemic situations. Studies varied in their collection of data and analysis of these other measures; for some it was not possible to disentangle mask/respirator wearing from other measures concomitantly applied (Annex 4). Other studies, through application of multivariate analysis and other analytic methods, were able to estimate the independent effect of mask/respirator wearing. Although the focus of our review and reporting of study results focused on the effect of mask/respirator wearing, we attempted to note other significant findings (Table 2). However, it was beyond the scope of the review to systematically consider and assess other interventions. It is somewhat paradoxical that whilst continued effort and resources are needed to assess the independent effect of masks and respirators on influenza transmission, their use would always be recommended in combination with other control measures.

The findings of this review highlight the many unanswered questions about the effectiveness of mask and respirator use in both healthcare and community settings. The relatively recent modest increase in both the number and comprehensiveness of studies is encouraging. However there is still an alarming lack of randomised trials in healthcare settings, and only a small number of observational studies with a specific focus on influenza are available. In addition, there is also a lack of studies addressing questions about a) whether the use of face masks by symptomatic individuals protects asymptomatic individuals not wearing a face mask and b) whether the use of face masks protects asymptomatic carers of symptomatic individuals in a care home setting. The

WHO's proposed public health research agenda for influenza prominently notes the urgent need for evidence to strengthen public health guidance and actions to limit the impact of influenza (40). The Institute of Medicine has conducted several reviews of respiratory protection for healthcare workers that have highlighted the need for research in this area (41-43). However, well designed studies in this field are challenging: they need to be adequately powered to assess potentially small differences between interventions and include an appropriate control group; their usefulness is enhanced by the collection of detailed versus non-specific exposure data; and objective monitoring of compliance and assessment of potential confounders are critical. Also, because infection control guidance in health care settings calls for the use of prescribed practices and personal protective equipment, it may be difficult ethically to establish control groups that do not adhere to these recommendations. The experience with the observational investigations of SARS, and recent evidence from observational studies following the 2009 pandemic suggest studies undertaken during or shortly after a crisis should be carefully planned and well resourced (many of the studies taken during SARS or the 2009 pandemic were poorly designed).

Strengths and weaknesses of the review

It is important to note the strengths and limitations of this review and update. The prescribed, narrow focus permitted review of a relatively small number of studies in great detail. However, we acknowledge a review that included interventions other than mask/respirator use, experimental laboratory and/animal human studies on mask/respirator efficacy, cost-effectiveness studies and the occurrence of adverse events would present a more comprehensive picture. Our analysis could be enhanced possibly with the application of quantitative techniques rather than a simple narrative approach. However, the range of study designs, pathogens, participants, interventions provided many opportunities for bias and confounding.

Several systematic reviews of interventions to limit transmission of respiratory viral infections and/or specifically influenza have been undertaken in recent years. Most have considered a range of interventions (44-48) while all have noted the paucity of data in this area. Within the boundaries established by our inclusion criteria, our search strategy captured many of the studies on face masks and respirators that other systematic reviews have identified. We noted some minor differences in our synopsis and assessment of individual studies compared with other investigators; for example we classified two studies as clinical trials while others considered them as prospective cohort studies (44). From the most recent review by Jefferson and colleagues (46), based primarily on the findings of the Loeb trial (study 5 in this review), it was concluded that while no evidence was found to demonstrate that N95 respirators were superior to face masks, facemasks/ respirators were the best performing intervention "across populations, settings and threats". The reviews by Jefferson et al also sought to pool odds and rate ratio's between the observational studies (focussing on SARS), whose methodology as we have demonstrated was problematic in various ways.

We sought to take careful note of how well exposures in various studies were detailed and if cases and controls were laboratory confirmed to avoid misclassification bias. Certainly we did not feel that such a heterogeneous group of studies could be combined even for SARS. The Jefferson reviews are very positive over physical interventions in general; treating respiratory viruses as a unitary whole they conclude that most physical interventions will reduce transmission (44-46). Aiello et al (47) arrived at the same general conclusion that there is some evidence that non-pharmaceutical interventions

(including wearing face masks separately or in combination with other prevention practices) can be efficacious for reducing rates of influenza and influenza-like illness, particularly in community settings (household, school and university residence hall study sites). Other systematic reviews are less certain in their conclusion. Gamage et al specifically addresses health care settings and takes a precautionary approach to barrier interventions (49).

Looking more widely in both the community and health care setting, Aledort et al (48) and recent reviews by Cowling (50, 51) recognise the limitations of the data and come to conclusions more similar to this review. The most recent review by Cowling et al (51) additionally includes studies which assess the technical capabilities of respirators as a barrier against infectious respiratory particles and identified that a properly fitted N95 respirator would dramatically enhance efficacy (52). Studies of this type, although not included in this update may provide some benefit for the entire evidence base on facemask/respirator use. However this review generally agrees with the studies included in this update and the conclusions reached. A final review, conducted by Rashid and colleagues (53) pool results from 15 studies including 5 RCTs (all studies included in our review) for comparison of 'plain surgical masks against no intervention'. The authors concluded there was no protective effect for masks against lab-confirmed influenza and while a protective effect against ILI outcome was observed across all studies in the meta-analysis, this was not significant. Constructing metadata from the range of studies, as performed by Rashid is questionable give the variability in study design; however they do agree that many of the studies suffered from significant limitations, mainly issues surrounding under-powering and small sample sizes.

Our 'bottom line' assessment of the available information for both healthcare and community settings is essentially unchanged from the previous HPA review and is similar to that of the recent review on face masks indicated above.

Conclusion

In conclusion there is limited data to support the use of face masks and/or respirators in healthcare and community settings. The effectiveness of masks and respirators is linked to consistent and correct usage; however, this remains a major challenge – both in the context of a formal study and in everyday practice. This update has demonstrated that new evidence has emerged (primarily for RCTs based in the community), however studies are still few and far between for influenza, particularly within the context of the 2009 pandemic, and there has yet to be any studies examining the behaviour of 'new' seasonal influenza (which may behave somewhat differently than the preceding seasonal influenza (50) . Hence continued research on the effectiveness of masks/ respirators and other associated considerations remains an urgent priority with emphasis being on carefully designed observational studies and trials best conducted outside the stress and strain of crises.

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Annex 1. Search terms for PubMed database search

[1] Respiratory viruses:

influenza OR influenza[tw] OR flu OR flu[tw] OR common cold OR common cold[tw] OR rhinovirus OR rhinovirus*[tw] OR adenoviridae OR adenovirus*[tw] OR coronavirus OR coronavirus infections OR coronavirus*[tw] OR respiratory syncytial viruses OR respiratory syncytial virus infections OR respiratory syncytial virus*[tw] OR respiratory syncitial virus[tw] OR parainfluenza virus 1 OR parainfluenza virus 2 OR parainfluenza virus 3 OR parainfluenza virus 4 OR parainfluenza[tw] OR para-influenza[tw] OR para influenza[tw] OR severe acute respiratory syndrome OR severe acute respiratory syndrome[tw] OR SARS[tw] OR acute respiratory infection*[tw] OR acute respiratory tract infection*[tw] OR influenza like illness OR influenza like illness[tw] OR ILI OR Severe acute respiratory infection OR Severe acute respiratory infection[tw] OR pandemic influenza OR pandemic flu

[2] Interventions and population groups:

masks OR mask*[tw] OR patient isolators OR personal protective equipment OR face protection OR N95 OR FFP2 OR FFP3 OR respirator OR home OR household* OR community OR nursing home OR nosocomial OR HCAI OR healthcare associated infection OR healthcare associated infections OR airborne precautions OR droplet precautions OR non-pharmaceutical intervention OR nonpharmaceutical intervention OR aerosol generating procedures OR healthcare workers OR healthcare workers OR HCW OR healthcare personnel OR healthcare personnel

Combining [1] AND [2] gave 5351 results for Search 1 and 317 results for Search 2.

The above search terms were combined to produce the following search on PubMed.

Search	Query
#64	Search (#37) AND #63
#63	Search ((((((((((((((((((((((((#38) OR #39) OR #40) OR #41) OR #42) OR #43) OR #44) OR #45) OR #46) OR #47) OR #48) OR #49) OR #50) OR #51) OR #52) OR #53) OR #54) OR #55) OR #56) OR #57) OR #58) OR #59) OR #60) OR #61) OR #62
#62	Search "healthcare personnel"
#61	Search HCW
#60	Search "healthcare workers"
#59	Search "aerosol generating procedures"
#58	Search "nonpharmaceutical intervention"
#57	Search "non-pharmaceutical intervention"
#56	Search "droplet precautions"
#55	Search "airborne precautions"

Search	Query
#54	Search "healthcare associated infections"
#53	Search "healthcare associated infection"
#52	Search HCAI
#51	Search nosocomial
#50	Search "nursing home"
#49	Search community
#48	Search household*
#47	Search home
#46	Search respirator
#45	Search FFP3
#44	Search FFP2
#43	Search N95
#42	Search "face protection"
#41	Search "personal protective equipment"
#40	Search "patient isolators"
#39	Search mask*[Text Word]
#38	Search masks
#37	Search ((((((((((((((((((((((((((((((((#1) OR #2) OR #3) OR #4) OR #5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13) OR #14) OR #15) OR #16) OR #17) OR #18) OR #19) OR #20) OR #21) OR #22) OR #23) OR #24) OR #25) OR #26) OR #27) OR #28) OR #29) OR #30) OR #31) OR #32) OR #33) OR #34) OR #35) OR #36
#36	Search "pandemic flu"
#35	Search "pandemic influenza"
#34	Search "severe acute respiratory infection"[Text Word]
#33	Search "severe acute respiratory infection"
#32	Search ILI
#31	Search "influenza like illness"[Text Word]
#30	Search "influenza like illness"
#29	Search "acute respiratory tract infection*"[Text Word]
#28	Search "acute respiratory infection*"[Text Word]
#27	Search SARS[Text Word]
#26	Search "severe acute respiratory syndrome"[Text Word]

Search	Query
#25	Search "severe acute respiratory syndrome"
#24	Search "para influenza"[Text Word]
#23	Search para-influenza[Text Word]
#22	Search parainfluenza[Text Word]
#21	Search "parainfluenza virus 4"
#20	Search "parainfluenza virus 3"
#19	Search "parainfluenza virus 2"
#18	Search "parainfluenza virus 1"
#17	Search "respiratory syncytial virus"[Text Word]
#16	Search "respiratory syncytial virus*"[Text Word]
#15	Search "respiratory syncytial virus infections"
#14	Search "respiratory syncytial viruses"
#13	Search coronavirus*[Text Word]
#12	Search "coronavirus infections"
#11	Search coronavirus
#10	Search adenovirus*[Text Word]
#9	Search adenoviridae
#8	Search rhinovirus*[Text Word]
#7	Search rhinovirus
#6	Search "common cold"[Text Word]
#5	Search "common cold"
#4	Search flu[Text Word]
#3	Search flu
#2	Search influenza[Text Word]
#1	Search influenza

Annex 2. Search terms for additional databases

For the update search were restricted for studies captured between June 2010 and November 2012. This required a time period restriction of years 2010-2012.

The Additional databases searched included:

Bandolier, the Cochrane Library Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) database), the NHS Economic Evaluation (NHS EED database), the UK Database of Uncertainties about the Effects of Treatments, the NHS Centre for Reviews and Dissemination (CRD) and the Cumulative Index to Nursing and Allied Health Literature (CiNAHL).

The following search terms were used for the additional databases;
(("respiratory viruses" OR influenza) AND (mask OR respirator OR N95 OR FFP OR FFP2 OR FFP3 OR "personal protective equipment")). [Limit to: Publication Year 2010-2012].

The following databases generated the following results (duplicate papers form PubMed excluded from the count).

[1] EMBASE and CiNAHL generated 175 results of which 16 were relevant

[2] DARE generated 3 results; none relevant

[3] HTA generated 1 results; none relevant

[4] NHS EED generated no results

[5] UK Database of Uncertainties about the Effects of Treatments generated no results

[6] CRD captured results from DARE and HTA: no new results

Annex 3. Data extraction elements for use of mask and respirator Reviewer

Study Identity
Title
Author
Journal/Year/Page

Study Eligibility

What type of study
Participants
Intervention: Mask/Respirator use?
Did study report specific outcomes?
Study included in review?
If study excluded - why?
Any further notes for exclusion:

Trial Characteristics
What type of study
Trial design
Setting
Type of participants
Country of Study
Time period of study
Disease studied
Number of groups
Method of randomisation (if applicable)
Method of concealment (if applicable)
Eligibility criteria
Time between enrolment & intervention
Adherence to intervention

RCT
Primary study aims
Secondary study aims (if applicable)
Sample size of control group
Sample size intervention group 1
Sample size intervention group 2 (as applicable)Type of intervention:
Sample size intervention group 3 (as applicable)Type of intervention:
Analysis
Outcome data:

Case-Control
Sample size of control group
Sample size of case group
Outcome data:

Cohort
Sample size of cohort group
Outcome data:

Annex 4. Synopsis of studies that met inclusion criteria but <u>not</u> included in the final review (excluded on quality n=17)

A. Randomized controlled trial

Investigator (Reference no.)	Study design and participants	Reason for exclusion	Reviewer comments
Murphy et al., 1981 (54)	Compared rates of RSV and other viral infections infection in U.S. paediatric nursing, medical and respiratory staff randomly assigned to either a hand washing alone group (N=30) or to a hand washing, gowning and masking group (N=28) when caring for 177 patients (49% with lab confirmed RSV) in respiratory isolation rooms	Effect of mask use could not be distinguished from gown use; type of mask not specified	Hospital exposures not precisely quantified; no attempt to assess community exposures Method of randomization not described; did not examine if HCWs who agreed to participate were different from HCWs who elected not to participate Younger staff and >30 hrs in patient rooms) correlated with illness (but not laboratory confirmed infection)

B. Quasi-experimental: non-randomized clinical trial

Investigator (Reference no.)	Study design and participants	Reason for exclusion	Reviewer comments
Agah et al., 1987 (55)	Children in U.S. with RSV assigned to one of two isolation categories and rates of RSV infection compared for 80 HCWs who wore masks and goggles when entering rooms of 6 patients with RSV; 61 HCWs who did not wear masks and goggles when entering rooms of 5 patients with RSV; and 27 HCWs who cared for 3 children with no respiratory illness	Effect of mask use alone was not evaluated; type of mask not specified	Small number of RSV patients available to study Method of assignment to study arms not described other than attempt to balance two groups by age and sex

C. Quasi-experimental: before-after study

Investigator (Reference no.)	Study design and participants	Reason for exclusion	Reviewer comments
Chen et al., 2004 (56)	Compared rates of SARS infection in HCWs caring for SARS patients in Taiwan prior to and after implementation of specified infection control precautions including N95 respirators, gown, gloves, cap and shoe covers	Effect of respirator use alone was not studied	Small number of HCWs studied; exposures poorly quantified
Hall et al., 1981 (57)	Evaluated rates of nosocomial RSV infection in infants and HCWs during two sequential periods when gowns and masks were used and not used	Effect of mask use could not be distinguished from gown use	No data on activities or procedures HCWs engaged in; did not assess potential community exposures

D. Observational: cohort study

Investigator (Reference no.)	Study design and participants	Reason for exclusion	Reviewer comments
Leung et al., 2004 (58)	Evaluated prospectively triage policy and risk-stratified infection control measures (including multi-component PPE) to prevent clinical SARS illness in paediatric HCWs in Hong Kong	Effect of mask or respirator use alone was not studied	No data on the number and types of contacts with SARS patients or unprotected exposures
Lu et al., 2006 (59)	Evaluated prospectively PPE use, clinical course and viral load in 4 HCWs and 12 non-HCWs with SARS linked to an index patient in a Taiwan hospital emergency department	Effect of mask use could not be distinguished from other PPE and hand washing	Small number of HCWs; study design did not control for factors other than PPE that might have affected transmission; numerator data only
Morgan et al., 2009 (60)	Evaluated retrospectively exposure to infectious material, PPE use (including masks and respirators) and oseltamavir prophylaxis and infection with avian influenza H7N3 during a poultry outbreak in England	Effect of mask or respirator use could not be distinguished from other PPE	Incomplete use of PPE associated with being a possible or confirmed case but subject to recall bias; confirmed infection only in index case
Ng et al., 2009 (61)	Retrospective questionnaire survey of Hong Kong nurses to assess influenza-like illness with PPE/infection control guidance compliance	Mask use and associated rates of influenza-like illness not reported	128 (96%) of 133 HCWs reported wearing a mask; exposure data not recorded

E. Observational: case-control study

Investigator (Reference no.)	Study design and participants	Reason for exclusion	Reviewer comments
Davies et al., 1994 (62)	Study carried out in the UK among dental surgeons, retrospectively evaluating an association between the use of masks as a preventative measure in their daily work and the prevalence of blood antibodies against different respiratory pathogens	The study does not show objective quantitative data on the use of non-pharmaceutical protective measures (masks)	The prevalence of seropositivity was not different in the dentists who used masks and eye spectacles compared to those who did not

F. Observational: cross-sectional study

Investigator (Reference no.)	Study design and participants	Reason for exclusion	Reviewer comments
Ang et al., 2010 (63)	This study carried out in a Singapore hospital during the first months of the 2009 pandemic evaluated the incidence of influenza infection and transmission within the hospital and its association with the use of face masks and practice of hand hygiene among HCWs	It is not possible to establish an association between both terms taking into consideration the study design	There are no data on adherence to guidelines for personal protective equipment during the various periods of the study
Cai et al., 2009 (64)	This study shows adherence to the use of preventative measures (PPE equipment) by people handling birds involved in an avian influenza A(H5N1) outbreak which happened in Germany in the spring of 2006	It is not possible to establish an association between the serological findings and the adherence to the use of PPE equipment	Small number of participants; recall bias is possible since the outbreak occurred three years before the paper was written
Cheng et al., 2010 (65)	This study conducted in Hong Kong during the initial months of the 2009 pandemic tried, through an infection control bundle, a series of strategic measures promulgated to enhance HCWs' awareness and compliance to these measures	The observation of cases is retrospective and there are not controls, thus the results are only approximate and cannot be used to infer any evidence	The methodology is not sound enough so as to render fully valid results, as it is based on the epidemiological analysis of clinical symptoms of the exposed persons without serological confirmation
Van Cauteren et al, 2012 (66)	This study uses a retrospective cross-sectional design (through telephone interviews) to assess influenza burden, health seeking behavior and	The study only looked at mask adherence by cases (not controls): it was therefore	Self-reported influenza only (no lab confirmation) and if using self-defined data should have defined as ILI; low

	hygienic measures (including face mask use) between May 2009 and April 2010. The target population was the 'general' French population.	impossible to infer if there was a protective effect.	response rate (57%); recall bias and non-inclusion of households with mobile phone only.
Tischendorf et al, 2012(67)	This study aimed to compare the distribution of face masks to respiratory infection and ILI (clinic and community levels) over a 31 week period from end of Oct 2009. Study site was a family practice clinic in Madison, US. Estimation of the annual need of face masks also calculated. A retrospective approach analyzing clinic data utilized.	Did not link transmission/risk of infection with mask use, rather examined distribution of mask use and acceptance of the practice in symptomatic individuals attending the clinic	No measurement of influenza transmission made; authors state that public more likely to accept/use facemasks in the study period because it followed on from the pandemic; no analysis conducted to assess demographics of study population
de Perio et al, 2012 (68)	This study conducted in Utah, US examined ILI prevalence/transmission, infection control practices and exposures amongst physicians (in–training) in affiliated hospitals. A retrospective random electronic survey and focus groups were the data collection methods utilized. The study was conducted during peak H1N1 pdm09 activity.	Only assessed participants infection control practices (including N95 respirator or surgical mask) when in contact with a patient (ILI or H1N1 pdm09 confirmed). Did not assess IC practices with participant ILI rates.	Very low response rate (42%); recall bias; self-reported exposures and IC practices; community exposures not assessed
Lousalot et al, (69)	This study examined transmission of H1N1 pdm09 and non-pharmaceutical intervention use (masks included) within household settings. All parents and guardians of a US based school (San Antonio, Texas) invited to participate following closure of the school; asked to complete internet or phone-based questionnaire	Parent/ guardian only reported there NPI practices- no analysis of whether these individuals a case or just household contact. Consequently, unable to determine effect of NPIs including facemask.	Potential misclassification of index cases/secondary cases; very low response rate (39%)- even lower response rate of individuals completing information on NPI use; all information self-reported & proxies used for all household member information; authors state *social desirability* bias may have been present
Yang et al (70)	This study reviewed respiratory infection prevalence and mask wearing and hand-washing amongst HCWs across 8 Beijing hospitals (winter 2007/08). Questionnaire administered to HCWs during April- May 2008 (exposures/mask use assessed for period Nov 2007- Feb 2008).	Only compared mask use against cotton mask- no assessment against non-exposed HCWs. Also CRI outcome (did not use more specific outcomes i.e. ILI)	Only level 2 and 3 hospitals included (lowest ranked hospitals i.e. level 1 excluded); self-reported data; recall bias; no community exposures measured

RSV= respiratory syncytial virus; SARS=severe acute respiratory syndrome; HCW=healthcare worker; PPE=personal protective equipment; IC= infection control; H1N1 pdmo09= 2009 pandemic influenza; CRI= clinical respiratory infection.

Annex 5. Findings in relation to SARS observational studies

A. Analysis and appraisal of SARS observational studies

Observational: case-control study

Investigator (Reference no.)	Study design and participants	Reported results	Comments
Chen et al., 2004 (20)	91 SARS IgG positive HCWs compared with 657 SARS IgG negative HCWs; both groups were 'frontline' HCWs who cared for SARS patients in two hospitals in Guangzhou China	Use of a double layer cotton mask (versus a single layer cotton mask) was protective against SARS infection in univariate analysis (OR 2.53, 95% CI 1.57-4.07); not significant in the multivariate analysis	**Reviewer**: Strength: All HCWs tested for SARS to reduce misclassification Limitations include possible recall bias as questionnaire survey conducted 4 months after outbreak; limited data on frequency and type of exposures to SARS patients; community exposures not assessed as possible confounder. **Author:** Limitations include limited generalisability as only 2 hospitals studied; ventilation in wards not objectively assessed and could be confounder; multiple PPE and other infection control measures used which were highly correlated and multivariate analysis may have omitted effective measures due to multi-co linearity; 10.8% of eligible HCWs who were 'off-duty' during the survey excluded
Lau et al., 2004 (21)	72 HCWS with SARS from 5 hospitals in Hong Kong compared with 144 matched controls; PPE use examined during 1) direct contact with SARS patient; 2) contact with SARS and non-SARS patients in general; and 3) no patient contact	Almost all HCWs wore either a N95 respirator or a surgical mask in all patient settings Inconsistent use of masks or respirators was not associated with a higher risk	**Reviewer:** Strengths include effort to assess exposures to SARS in hospital and community, including performance of high risk procedures (i.e. intubation, suction, CPR) Possible risk of misclassification bias in

		for SARS in unadjusted univariate analysis in any of the 3 contact settings; inconsistent use of ≥3 types of PPE (including masks) a significant predictor of SARS Multivariate analysis found perception of inadequate supply of PPE, <2 hours of infection control training and inconsistent use of PPE were independent risk factors for SARS	that different methods of interview (self versus external interviewer) used for different types of HCWs **Author**: Strengths include relatively large sample size; high (93.5%) participation rate among probable and suspect SARS cases; and control of exposure to potential confounding factors Limitations include some risk of recall bias although interviews of infected HCWs usually within one week of hospitalisation; bias associated with case group's attribution of their infection to external factor (e.g. inadequate supplies) in contrast to controls; lack of serologic testing to confirm non-infection in controls (although no asymptomatic infections found in serologic survey of 674 HCWs working in the same hospital)
Nishiura et al., 2005 (22)	Two time periods associated with a specific hospital: Period 1: Time from admission of an index case to onset of secondary cases: 25 laboratory-confirmed SARS cases (>20 yrs) in Hanoi compared with 90 controls who were a mix of HCWs and relatives of patients determined not to have 'trivial' exposure to SARS patients Period 2: Time from suspicion of nosocomial spread to closure of hospital and subsequent reopening with strict isolation procedures, quarantine of HCWs and increased use of PPE: 4 laboratory-confirmed SARS cases compared with	Period 1: univariate analysis found masks (OR 0.3 95%CI 0.1-0.7) and gowns (OR 0.2 (95%CI 0.0-0.8) protective; in logistic regression analyses only masks protective (OR=0.29, 95%CI CI 0.11-0.73) Period 2: use of masks (OR<0.1, 95%CI CI 0.0-0.3) and gowns (p=0.010, OR and CI not calculable) associated with non-infection for doctors	**Reviewer:** Strength: validation of survey questions attempted by repeat administration Limitations include discrepancies in number of cases and controls in text and Table 2; although efforts made to quantify exposures, approach was imprecise (e.g. 'many times' included persons who cared for/lived with SARS patients as well as those who came within one metre; serologic testing for SARS not done to detect infected asymptomatic controls (some studies

	26 controls with only physicians and nurses in both groups	and nurses; 1 (25%) of 4 cases and 25 (96%) of 26 controls used all measures (hand washing and masks, gowns and gloves)	have found ~10% of HCWs who had contact with SARS patients were seropositive but asymptomatic) (19) **Author:** Strengths include used multivariate analysis to minimise selection bias associated with non-matched case-control design Limitations include possible recall bias, especially when exposure has intuitive link with outcome; possible random misclassification as surveys completed 1 year after outbreak; frequent use of masks among controls may have underestimated protective effect; small number of cases in 2nd time period precluded stratified analysis; thus protective effect of masks may include effects of other concomitant changes as potential confounders such as reduced frequency of contacts and quarantine of HCWs
Nishiyama et al., 2008 (23)	Risk factors for serologically confirmed SARS infection examined among 85 case and control HCWs at a Hanoi hospital who had direct contact with SARS patients	Multivariate logistic regression analysis found significant risk for SARS among HCWs who never wore mask compared to those who always wore a mask (adj OR 12.6 (95% CI 2.0-80.0, p<0.01)	**Reviewer:** Strength: All HCWs tested for SARS to reduce misclassification Limitations include possible recall bias as interview was 7 months after outbreak; lack of information about how/why 85 HCWs (a subset of all HCWs that were enrolled) were selected for the case-control analysis and how these HCWs may have differed from non-selected HCWs; non-specificity of exposure (defined as physical contact with SARS

			patient or excretions); possible confounding as community exposures to SARS not addressed; limited generalisability as study hospital had large outbreak of SARS
Seto et al., 2003 (24)	13 SARS-infected HCWs with no community exposures compared with 241 HCWs without clinical SARS, all of whom reported direct contact (within I metre) of 11 known SARS patients in 5 hospitals in Hong Kong	Univariate analysis found HCWs who used surgical masks or N95 respirators, gowns or hand washing less likely to develop SARS; logistic regression analysis showed only use of masks (i.e. paper, surgical N95 respirator grouped together) was significant (OR 13, CI 3-60) None of 69 HCWs who consistently used surgical mask, respirator, gown and hand washing developed SARS	**Reviewer:** Limitations include exposure only generally defined as 'coming within 1 metre of a SARS patient;' comparability of cases and controls not assessed and cannot exclude differences in specific types of exposures between cases and controls; multiple PPE measures used and likely correlated; small number of cases; community exposures not assessed as possible confounder for controls; possible misclassification of some controls as serological testing not done Opportunities for bias include exclusion of HCWs from a hospital associated with an outbreak reportedly traced to a patient receiving nebulizer therapy and non-response of 419 HCWs (15% of those eligible to participate) most of whom worked night shift at time of survey **Author:** Possible recall bias as questionnaire survey conducted a month after cases first identified in China
Teleman et al., 2004 (25)	Evaluated risk factors for serologically-confirmed SARS among 36 clinically ill case-HCWs exposed to 3 highly infectious (i.e. 'super spreader') source patients and 50 clinically well	Adjusted logistic regression analyses found that wearing N95 respirator during each patient contact (adj OR 0.1,	**Reviewer:** Strength: detailed exposure data sought (e.g. frequency and type of procedures)

	control-HCWs who came within 1 metre of serologically-confirmed SARS patients in Singapore hospital	95% CI 0.02-0.86, p=0.04) and hand washing after patient contact (adj OR 0.07, 95% CI 0.008-0.66, p=0.02) were protective	Limitations include lack of serological testing of control-HCWs and possible misclassification if asymptomatic SARS infections occurred in controls; no assessment of community exposures as possible confounder **Author**: Strengths include magnitude of OR unlikely to reflect recall bias related to PPE; opportunity for recall bias reduced since study done very close to hospital outbreak Limitations include no adjustment for possible confounders such as differences in exposure (e.g. exposure to 'super spreader' index patients, lack of viral load data for patients) which could explain wide variability in observed infectiousness across patients and outbreaks; difficulty in HCWs' recall of precise exposure data; small sample size
Lau et al., 2004 (26)	330 probable SARS cases (>16 years) in Hong Kong with an 'undefined' source of infection compared with 660 controls recruited by random telephone survey matched for age, sex and reference time for behaviours in question	Matched multivariate analyses found using a mask frequently in public places 27.9% of 330 cases versus 58.7% of 660 controls (OR=0.36, 95% CI 0.25-0.52); washing one's hands >10 times a day (OR=0.58, 95% CI 0.38-0.87) and disinfecting living quarters (OR=0.41, 95% CI 0.29-0.58) were protective; these factors remained protective when a subset of 118 cases analysed	**Reviewer:** Limitations include possible misclassification of cases and controls as laboratory testing not done **Author:** Strengths include collection of most data within one month of case-patient's onset of fever; minimisation of potential confounding due to exclusion of cases with exposure to known sources of infection Limitations include nonspecific nature of questions about exposures and potential protective measures which could result in

		who had not visited any places (e.g. hospital, mainland China) where community acquisition of SARS more likely	inconsistent interpretation; collection of information from household proxies if patients unable to answer questions
Wu et al., 2004 (27)	Evaluated retrospectively 94 unlinked, probable clinical SARS cases without reported contact with other SARS cases and 281 community-based age and sex matched controls in Beijing recruited by sequential digit dialing	Multivariate analysis found sometimes and always wearing a mask when going out of the house protective (matched OR 0.4, 95% CI 0.2-0.9, p 0.03 and OR 0.3, 95% CI 0.1-0.6, p=0.002, respectively)	**Reviewer**: Strengths include sufficiently powered study design; co linearity and pair-wise interactions evaluated for all variables in the final model Limitation: lack of specific information about exposures to SARS in the community **Author:** Limitations include high rate (50%) of non-participation by prospective cases and possibility of self-selection; limited laboratory confirmation of clinical diagnosis among cases suggests that for many SARS was not likely cause of their illness; recall bias (interviews for some participants 6-10 weeks after period of interest) may have resulted in misclassification of behavior frequencies; representativeness of controls unknown
Observational: cohort study			
Loeb et al., 2004 (28)	Retrospective cohort among 43 nurses who worked in a Toronto hospital ICU or CCU when a laboratory confirmed SARS patient was in the unit during March 2003 to assess risk factors for SARS infection; analysis limited to 32 nurses who entered patient's room at least once.	3 (13%) of 23 nurses who consistently wore a mask (either surgical or N95 respirator) developed SARS compared to 5 (56%) of 9 nurses who did not consistently wear either (RR 0.23, p=0.02)	**Reviewer:** Strengths include serological confirmation of SARS infection in index patients and ill nurses; exposure data on type and duration of patient care activities and type and frequency of PPE use sought Limitations include too small a sample size to assess SARS risk by procedure

				2 (13%) of 16 nurses who consistently wore a N95 respirator developed SARS compared with 1 (25%) of 4 nurses who consistently wore a surgical mask (RR=0.50, p=0.51)	and if mask/respirator worn during procedure; potential confounding due to community exposures not explored; serological confirmation of non-infection status of asymptomatic nurses not done **Author:** Strength: since use of PPE not standardised during study period, possible to asses effect of individual types of PPE; PPE use variable as nurses often unaware that patients had SARS Limitations include possible recall bias but minimised by verifying information such as patient care activities using medical records when possible; small sample size limits inferences that can be drawn	

RSV= respiratory syncytial virus; SARS=severe acute respiratory syndrome; HCW=healthcare worker; PPE=personal protective equipment; RT-PCR=reverse transcription polymerase chain reaction; ILI=influenza-like illness; CPR=cardiopulmonary resuscitation; ICU=intensive care unit; CCU=coronary care unit

B. Summary of case control studies evaluating mask/respirator use and SARS

Investigator (Reference no.)	Type of mask evaluated	Interval from outbreak to study	Exposure information	Evaluation of potential confounding factors	Case and control issues	Reported results
Chen et al., 2004 (17)	Double (versus single) layer cotton mask	4 months	Subjects were 'frontline' HCWs who cared for SARS patients Survey asked about frequency of wearing	Multiple logistic regression analysis controlled for age, gender, marital status, educational level, professional title and	10.8% of eligible frontline HCWs who were not on duty during the survey excluded	Double layer cotton mask (versus a single layer cotton mask) protective in univariate analysis but not significant in the multivariate analysis

			types of PPE, layering of PPE, limited number of specific patient care activities (i.e. performing tracheotomy, intubation, caring for 'super spreader' patient) and method of ventilation	work department Community exposures to SARS not assessed as possible confounder	Cases and controls serological tested	
Seto et al., 2003 (21)	Paper mask, surgical mask and N95 respirator	~ 1 month	Defined generally as coming within 1 metre of 11 laboratory-confirmed SARS index patients	No information about comparability of cases and controls or if any potential confounding factors controlled for (e.g. possible differences in intensity of exposure to SARS patients)	Clinically diagnosed case-HCWS serologically-confirmed; clinically-well control-HCWs not tested HCWs from a hospital with outbreak reportedly traced to a patient receiving nebulizer therapy and 15% of eligible HCWs who did not return questionnaires were excluded	Logistic regression analysis showed only use of masks (i.e. paper, surgical and N95 respirator grouped together) significant; univariate analysis found surgical masks, N95 respirators, gowns and hand washing significantly associated with non-infection
Lau et al., 2004 (18)	Surgical mask N95 respirator	Usually within 1 week (at least for cases who were interviewed whilst in hospital)	Three groups of HCWs defined: 1) direct contact with SARS patient; 2) contact with SARS and non-SARS patients in general; and 3) no patient contact HCWs also asked about performance of high risk procedures (i.e.	Use of a matched study design Multivariate analysis controlled for varying levels of exposure to SARS patients in community and hospital settings	93.5% of known HCWs with SARS participated in study Lack of serologic testing to confirm non-infection in controls (although no asymptomatic infections found in serologic survey of	Almost all HCWs wore either a N95 respirator or a surgical mask in all patient settings Inconsistent use of masks or respirators was not associated with a higher risk for SARS in unadjusted univariate analysis; multivariate

			intubation, suction, CPR)		674 HCWs working in the same hospital)	analysis found inconsistent use of >1 type of PPE (including masks) an independent risk factor for SARS
Nishiura et al., 2005 (19)	Surgical masks	Up to 1 year after onset of epidemic	Frequency of contact defined as 'many times' included persons who cared for/lived with SARS patients as well as those who came within 1 metre	Analysis included investigation of interactions between significant behaviour and other variables in univariate analysis and performance of multiple logistic regression analysis Small number of cases in 2nd time period precluded stratified analysis; thus protective effect of masks may include effects of other potential confounders such as reduced frequency of contacts and quarantine of HCWs	Lack of serologic testing to confirm non-infection in controls Contact tracing investigations identified controls as persons thought to have contact with confirmed cases inside the hospital; excluded persons with 'trivial' contact such as exposure during transport of SARS patients or in casualty reception room Effort to minimize recall bias in period 2 included restricting analysis to those with probable contact to cases whose incubation period occurred after beginning of period 2 and to include only doctors and nurses as cases and controls	Period 1: logistic regression analyses found that only masks were protective Period 2: use of masks and use of gowns associated with non-infection; however, 1 (25%) of 4 cases and 25 (96%) of 26 controls used all measures (masks, gowns, gloves and hand washing)

Nishiyama et al., 2008 (20)	Masks	7 months after beginning of SARS epidemic	Contact included direct and indirect; direct contact defined as physical contact with a SARS patient or excretions	Community exposures to SARS not assessed as possible confounder	Lack of information about how/why 85 HCWs (a subset of all HCWs that were enrolled) were selected for the case control analysis and how these HCWs may have differed from non-selected HCWs Cases and controls serologically tested	Multivariate logistic regression analysis found significant risk for SARS among HCWs who never wore mask compared to those who always wore a mask
Teleman et al., 2004 (22)	N-95 respirators	Soon after hospital outbreak	Case-HCWs had exposure to one of 3 hospitalised 'super-spreader' patients; control-HCWs had history of being within 1 meter of a laboratory-confirmed SARS patient Detailed exposure data sought (e.g. frequency and type of procedures)	Community exposures to SARS not assessed as possible confounder	Lack of serologic testing to confirm non-infection in controls	Adjusted logistic regression analyses found that wearing N95 respirator during each patient contact and hand washing after patient contact protective; contact with respiratory secretions associated with increased odds of infection
Lau et al., 2004 (24)	Mask	Collection of most data within one month of case-patient's onset of fever	Case patients had no defined source of infection; cases and controls queried about potential geographic exposures (e.g. visiting a hospital, crowed places) and contact with certain groups of people (e.g.	Use of a matched study design Minimisation of potential confounding due to exclusion of cases with exposure to known sources of infection	Neither cases nor controls laboratory-confirmed and thus subject to misclassification Collection of information from household proxies if	Matched multivariate analyses found using a mask frequently in public places, washing one's hands >10 times a day and disinfecting living quarters were protective factors

			medical personnel, hospital visitors) and possible protective factors (e.g. masks wearing, hand washing disinfection)		patients unable to answer questions	
Wu et al., 2004 (25)	Mask	Longest interval ~ 6-10 weeks after case's onset	Cases and controls asked about potential risk factors for exposure (e.g. visiting healthcare facility) and use of masks	Use of a matched design	High rate (50%) of non-participation by prospective cases and possibility of self-selection; limited laboratory confirmation of clinical diagnosis among cases suggests that for many SARS was not likely cause of their illness; representativeness of controls unknown	Multivariate analysis found sometimes and always wearing a mask when going out of the house protective

RSV= respiratory syncytial virus; SARS=severe acute respiratory syndrome; HCW=healthcare worker; PPE=personal protective equipment; RT-PCR=reverse transcription polymerase chain reaction; ILI=influenza-like illness; CPR=cardiopulmonary resuscitation; ICU=intensive care unit; CCU=coronary care unit

C. Analysis and interpretation of SARS observational studies

A case-control study design was the approach that investigators used to evaluate risk factors for SARS among hospital-based healthcare workers (Tables 2 and 3). All but two (20, 21) of these studies reported that wearing masks and/or respirators seemed to appear to protect workers from acquiring SARS (22-25).

Chen found that a double layer cotton mask was protective against SARS in a univariate analysis of 'frontline' healthcare workers who cared for SARS patients in Guangzhou, China (20). Although use of a double layer mask was not significant in the multivariate analysis, the investigators suggest that the use of multiple pieces of personal protective equipment and other infection control measures were highly correlated and the analysis may have omitted effective measures due to multi-co linearity (20).

Two studies evaluated SARS transmission among healthcare workers in five hospitals in Hong Kong. The first study compared 13 SARS-infected healthcare workers with 241 healthcare workers without clinical SARS, all of whom reported direct contact (i.e. were within one metre) of 11 known SARS patients (24). Workers who consistently used either a mask or respirator were less likely to become infected. Logistic regression analysis showed that only the use of masks (i.e. paper masks, surgical masks and N95 respirators grouped together) was significant. Importantly, the comparability of cases and controls was not detailed and could not exclude differences in specific types of exposures between cases and controls. In the second study, 72 healthcare workers with SARS from these five hospitals were compared with 144 matched controls (21). Almost all healthcare workers reported wearing either a N95 respirator or a surgical mask and there were no differences between the case and control groups in the proportion of workers who performed high-risk procedures. The univariate analysis did not show an increased risk for SARS associated with inconsistent use of masks or N95 respirators; a multivariate analysis that controlled for varying levels of exposure to SARS patients in hospital and community settings found that inconsistent use of $\geq$3 types of personal protective equipment (including masks) was a significant predictor of SARS.

Two studies were conducted in Hanoi, Vietnam. The first examined the relationship between SARS and increasingly stringent infection control measures that were implemented during two time periods in one hospital as awareness of the potential for nosocomial transmission for SARS increased (22). Masks (respirators were not available) were found to be protective at both periods. Importantly, the control group was not tested for evidence of antibodies to the SARS coronavirus to confirm the diagnosis of SARS which may have resulted in misclassification bias. Approximately 10% of asymptomatic healthcare workers in Hanoi who had contact with SARS patients were found to be seropositive in another study (20). The second study of healthcare workers in a Hanoi hospital used serological testing to confirm the case and control status of healthcare workers. Multivariate logistic regression analysis found a significant risk for SARS infection among healthcare workers who never wore a mask compared to those who always wore a mask (23).

Teleman compared healthcare workers exposed to one of three hospitalised 'super spreader' patients in a Singapore hospital with control healthcare workers who had a history of being within one meter of a laboratory-confirmed SARS patient (25). Serologic testing to confirm non-infection in the controls was not undertaken in this study. Adjusted

logistic regression analyses found that wearing a N95 respirator during each patient contact and hand washing after patient contact were protective.

A retrospective cohort study was undertaken among 43 nurses who worked in two Toronto hospital intensive care units when laboratory-confirmed SARS patients were hospitalised in the units (26). Nurses who consistently wore a mask (either a surgical mask or a N95 respirator) were observed to have a nearly 80% reduction in risk for infection. The relative risk of SARS for nurses who consistently wore a N95 respirator when caring for SARS patients was half that for nurses who consistently wore a surgical mask; however, the difference was not significant due to a small sample size. The study analysed occupational SARS risk in the early days of the Toronto epidemic when stringent use of personal protective equipment had not yet been implemented and nurses were often not aware that their patients had SARS; as the authors indicate, this facilitated assessment of individual types of personal protective equipment.

The two community-based studies used a matched case-control study design to evaluate probable, clinical cases of SARS with an undefined source of infection with randomly telephone-recruited matched controls (27, 28). Each study found that using a mask outside of the home on a regular basis was protective although the level of exposure to persons with SARS was unknown. Laboratory confirmation of cases and controls was not routinely employed in either study. Wu and colleagues did endeavour to collect samples for serological testing of clinical cases; samples were obtained for about a third of the cases and only a quarter of them tested positive for SARS indicating that exposure to SARS was limited in the study group (28).